The Bowling Green Study of the Primary and Secondary Prevention of Atherosclerosis: Descriptive Analysis, Findings, Applications, and Conclusions[1]

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ABSTRACT. **The Bowling Green Study (BGS) is a 16 year ongoing study of the primary and secondary prevention of atherosclerotic disease (ASD). This paper provides a descriptive analysis of the study, discusses the evolution of the cholesterol retention fraction (a new lipid predictor), and presents a series of tables showing the physical and metabolic characteristics of those patients who developed clinical atherosclerotic disease during the first 16 years of the study.**

The BGS has evolved a predictor of the lipid portion of ASD risk superior to those previously used. This predictor, termed the cholesterol retention fraction (CRF), estimates the cholesterol entering the arterial wall and thus promoting the ASD process as well as the cholesterol being removed from the arterial wall and thus counteracting the ASD process. The BGS demonstrates that it is the balance between these two factors that is crucial to the ASD process; it is the relative excess of cholesterol entering the artery wall compared to the relative paucity of cholesterol being removed from the artery wall that promotes ASD and reversal of ASD depends on reversing this process, such that more cholesterol exits the artery wall than enters it.

The basic ASD process is accelerated by cigarette smoking, a risk factor that is capable of producing clinical ASD in the absence of cholesterol imbalance. Indeed, the BGS data reveal that cigarette smoking counteracts the anti-ASD advantage conferred by low CRF. This advantage is also compromised by hypertension but, whereas cigarette smoking exerts its effects in younger people, hypertension exerts its effects in older people (who are less likely to smoke).

The three risk factors (CRF, smoking, hypertension) have been combined by the BGS into an instrument that allows with high accuracy the prediction of the population at-risk for ASD at a single pass. This instrument is termed the BGS Graphs, which not only identify the at-risk population but also guide therapy to reverse the ASD process. The CRF portion of the BGS Graphs has been validated against 15 international studies that have assessed the progression or regression of ASD in response to therapeutic intervention.

Finally, recommendations have been made, based on BGS findings, as to the use of lipid-reducing medications to reverse ASD. In addition, recommendations have been offered concerning the treatment of hypertension utilizing the BGS Graphs to guide antihypertensive therapy such that lipids are not adversely affected while high blood pressure is being lowered. These recommendations are applied to the BGS Graphs to demonstrate how the risk of future ASD may be minimized.

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INTRODUCTION

According to the American Heart Association, atherosclerotic disease (ASD) is the leading cause of death of adult Americans, killing 978,500 people in 1986, the latest year for which such data are available (Heart Facts 1988). Of these deaths 524,100 were caused by heart attacks and 147,800 were the result of strokes. The chief causes of ASD are well known and consist of blood cholesterol, cigarette smoking, and hypertension (Criqui 1986, Fraelecher 1973, Levy 1984, Oliver 1973). Theoretically, if the causes of ASD are well known, then correction of the underlying etiologies should lead to the primary and secondary prevention of ASD. Indeed, it is the opinion of at least one physician-worker in the field that "in theory and principle, the problem of the disease atherosclerosis has been solved" (Samuel 1986). The purpose of the present paper is to provide a descriptive analysis and the results of a study whose goal is the primary and secondary prevention of ASD.

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MATERIALS AND METHODS

Study Site

The Bowling Green Study (BGS) is an ongoing investigation of the primary and secondary prevention of ASD. The BGS began in November 1974 and at the time of submission of this paper was over 16 years old. The patient population consisted of a private practice of family medicine in Bowling Green, OH. The patient population as of 1 January 1991 numbered 8,606 people of which 4,144 were men and 4,462 were women. These patients ranged in age from newborns to nonagenarians (Table 1). Since the BGS is ongoing, new patients are being added to the study each year.

Bowling Green is a small college town in northwest Ohio, about 20 miles south of Toledo. It is the county seat of Wood County, and in 1990 had a population of about 12,000 people (1990 census). The students of Bowling Green State University added an additional 16,000 to the populace, and virtually all of these people received medical care from the Bowling Green medical community. Bowling Green was likewise the main source of medical services for the rest of the residents of Wood County, an additional 85,000 people. The populace was virtually all Caucasian, the chief minority being Mexican-Americans.

TABLE 1

Patient population demographics, by age groups. "Age group" is determined by age at initial presentation to the Bowling Green Study (BGS) in the 4 November 1974 – 1 January 1991 time frame.

AGE GROUP (Years)	MALE	FEMALE	TOTAL
0-9	462	468	950
10-19	830	849	1,679
20-29	1,536	1,588	3,224
30-39	606	590	1,196
40-49	283	302	585
50-59	196	239	435
60-69	130	145	275
70-79	71	104	175
80-89	28	48	76
90	2	9	11
TOTAL	4,144	4,462	8,606

Asian-Americans and African-Americans were also represented, though only in small numbers.

Virtually all patients were free-living in the community. Most were employed by the university or by numerous small industries located within the town. Many of those patients living outside the town were engaged in agriculture.

Patient Measures

Almost all patient data were taken from outpatient visits. Each time a patient presented for medical care a full set of vital signs were taken by the office nursing personnel. These vital signs included blood pressure (BP), pulse, respiratory rate, height, and weight. The BP was measured in the sitting position, usually in the right arm. Diastolic BP was measured in the fifth phase. Lipid data were obtained from patients who had fasted 12-14 hours, and included total cholesterol (C_T), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and triglycerides (TG). Occasionally, C_T and HDL were determined in patients who were not fasting. Glucose tolerance data were determined in the fasting state and two hours postprandial. The latter test was determined precisely two hours after ingestion of the standard breakfast, which consisted of one glass of orange juice, one bowl of cereal with milk and sugar, and three pieces of toast with butter and jelly. This meal consisted of 100 g of carbohydrate and was consumed within a 15 min time span.

All laboratory data were collected and measured by the same regional laboratory, based in Toledo, OH, using the Technicon AutoAnalyzer (1975-1985) or the RA 1000 (1985 to present). The Technicon AutoAnalyzer used the cholesterol esterase method as described in the Technicon Method No. SM4-0139J86 of September 1986, as did the RA 1000. The HDL fraction was measured as supernatant cholesterol after phosphotungstic acid precipitation. Triglycerides were measured by the enzymatic blank, corrected, as described in the Technicon Method No. SM4-0173G90 of July 1990. The LDL fraction was calculated by the standard Frederickson formula:

$$LDL = C_T - HDL - TG/5,$$

where TG were less than 500 mg/dl. Plasma glucose was measured by the glucose oxidase reaction (Trinder method). Quality control was done on a daily and weekly basis. Calibration was done by CDC standard. Because LDL and HDL data were not available to the BGS until January of 1978, lipid data obtained prior to this date were limited to C_T and TG.

The BGS used the body mass index (BMI) as its measure of obesity. The BMI was calculated by the formula:

$$BMI = \text{Weight (kg)} / [\text{Height (m)}]^2.$$

Follow-up on these patients was provided by direct continuous patient care and by follow-up interviews in hospital, by telephone interviews, or by review of medical records. Full follow-up is not available on all 8,606 patients. Therefore, some cases of ASD may have escaped BGS detection. This is regrettable, but unavoidable, in a study of this nature. In any event, all patients known to have suffered some form of ASD were included in this paper (Tables 2-5).

TABLE 2

Distribution of Bowling Green Study (BGS) patients with atherosclerotic disease (ASD) of the heart (ASHD), brain (ASBD), and peripheral vasculature (ASVD), during the 4 November 1974 – 1 January 1991 time frame.

ASD TYPE	MALE	FEMALE
ASHD	165 (4.0%)	168 (3.8%)
ASBD	60 (1.4%)	55 (1.2%)
ASVD	39 (0.9%)	24 (0.5%)
ALL ASD	196 (4.6%)*	195 (4.3%)*
TOTAL BGS Population	4,144	4,462

Numbers in parentheses indicate prevalence rate.
*Some patients had multiple system disease

Lipid Predictions

When this study began in 1974, the BGS followed the guidelines of the Framingham Study, using C_T and TG as its lipid predictors (Kannel et al. 1971). In the BGS experience, however, C_T was only of value in predicting subsequent ASD when C_T exceeded 250 mg/dl and TG was not of value in predicting future ASD.

The landmark paper by Miller and Miller (1975) re-established the role of HDL in ASD when C_T levels were normal; LDL was found to be that portion of cholesterol entering the artery wall, whereas HDL was found to be that portion of cholesterol being removed from the artery wall. ASD could thus be described as the result of an "overload" of cholesterol entering the artery wall (LDL excess) or to a deficiency in the cholesterol-removal mechanism (HDL deficiency). Hence, when LDL and HDL levels became available to the BGS in 1978, they were used as lipid predictors. (Patients whose lipid data was obtained prior to 1978 had only C_T and TG measured.) Subsequently, some patients with high HDL developed ASD as did some

TABLE 3

Distribution of patients with atherosclerotic heart disease (ASHD) as to presenting ASHD manifestation during the 4 November 1974 – 1 January 1991 time frame.

SEX	N	AMI	AP	ASHD HX	ACI	CHF	TREADMILL/ANGIOGRAM POSITIVE
Male	165	45 (27%)	23 (14%)	72 (44%)	5 (3%)	13 (8%)	7 (4%)
Female	168	19 (11%)	45 (27%)	60 (30%)	3 (2%)	35 (21%)	5 (3%)

Numbers in parentheses indicate the percentage of patients with each manifestation.

Abbreviations are as follows: AMI = acute myocardial infarction, AP = angina pectoris, HX ASHD = history of ASHD, ACI = acute coronary insufficiency, CHF = congestive heart failure. All terms are defined fully in Appendix I.

TABLE 4

Distribution of patients with atherosclerotic brain disease (ASBD) as to presenting ASBD manifestation during 4 November 1974 – 1 January 1991 time frame.

SEX	N	HCVA	TCVA	TIA	ASBD HX	ACS
Male	60	—	13 (22%)	9 (15%)	24 (40%)	14 (23%)
Female	55	2 (4%)	18 (33%)	18 (20%)	19 (35%)	5 (9%)

Numbers in parentheses indicate percentage of patients with each manifestation.

Abbreviations are as follows: HCVA = hemorrhagic cerebrovascular accident, TCVA = thrombotic cerebrovascular accident, TIA = transient ischemic attack, HX ASBD = history of ASBD, ACS = asymptomatic carotid stenosis. All terms are defined fully in Appendix I.

TABLE 5

Distribution of patients with atherosclerotic vascular disease (ASVD) as to presenting ASVD manifestation during 4 November 1974 – 1 January 1991 time frame.

SEX	N	TAA	AAA	ASPVD	ASVD HX
Male	39	2 (5%)	14 (36%)	19 (49%)	4 (10%)
Female	24	—	2 (8%)	20 (83%)	2 (8%)

Numbers in parentheses indicate percentage of patients with each manifestation.

Abbreviations are as follows: TAA = thoracic aortic aneurysm, AAA = abdominal aortic aneurysm, ASPVD = atherosclerotic peripheral vascular disease, HX ASVD = history of ASVD. All terms are defined fully in Appendix I.

patients with low levels of LDL. Investigation of these patients revealed that those with high levels of HDL also had very high levels of LDL, and that those with low levels of LDL also had very low levels of HDL. The BGS therefore adopted the LDL:HDL ratio as its lipid predictor. However, the LDL:HDL ratio did not prove to be the best lipid predictor. A new lipid predictor was designed to reflect the balance between incoming LDL cholesterol and the HDL cholesterol being removed, the difference representing the cholesterol remaining in the arterial wall. Thus the concept of the Cholesterol Retention Fraction (CRF) was devised:

$$\frac{\text{LDL - HDL}}{\text{LDL}}.$$

The CRF represents the best available approximation of the cholesterol accumulating within the artery wall, expressed as a percentage of the incoming LDL.

Inspection of the BGS age-sex register of ASD patients (Appendix I, Tables 6-11) reveals that HDL cannot compensate for excess LDL. When LDL levels exceed 170 mg/dl (4.4 mmoles/L), even high levels of HDL do not afford protection. Thus the CRF is abnormal at levels of 0.70 or higher, or at any level if LDL ≥170 mg/dl. These two conditions define the Cholesterol Threshold (C Thr), above which the patient is at risk for the lipid portion of ASD risk.

Drug Intervention

The BGS therapeutic approach to patients who exceed the C Thr is initially a combination of diet and/or exercise. Such an approach often does not succeed in reducing the CRF/LDL below the C Thr. After a trial of a minimum of one month of nonpharmacologic therapy, hypolipidemic medications are routinely employed to bring the CRF/LDL below the C Thr. In cases where the C Thr is markedly elevated, appropriate medications are begun initially along with diet and exercise.

RESULTS

BGS Graphs

The BGS developed a screening tool that accurately identified those people with a high probability of developing

clinical ASD within the first eight decades of life. This tool, known as the BGS Diagnostic and Therapeutic Graphs (BGS Graphs), also provided the treating physician with a guide to treatment of the leading causes of ASD. In devising this tool, several combinations of risk factors were examined for predictive ability, but only one combination showed any relationship that allowed prediction: the combination of the CRF, cigarette smoking habit, and systolic blood pressure (SBP), the three main ASD risk factors. A clear-cut relationship was apparent when the CRF was plotted versus the SBP in never-smokers (Fig. 1a), ex-smokers (Fig. 1b), and current smokers (Fig. 1c) for patients aged less than 80 years. For the purpose of plotting values the CRF was placed on the ordinate and the SBP on the abscissa.

In each figure a mainstream of sequence of ASD patients was detected, as well as a zone in which there were few if any plots. The area of the graph in which most plots fell defined the "danger zone," and the zone in which few plots fell defined the "minimum risk zone." While the minimum risk zone increased in size as one progressed from smokers (Fig. 1c) to ex-smokers (Fig. 1b) to never-smokers (Fig. 1a), only in the latter graph was the distinction sufficiently clear-cut to permit precise definition of the two zones by a line termed the ASD Threshold Line. However, the benefits of having the patient stop smoking were obvious—i.e., a bigger minimum risk zone occurred in past-smokers (Fig. 1b) than in current smokers (Fig. 1c).

The vast majority of patient plots (Fig. 1a) fell above the threshold line. Of the 64 plots on the graph, only 10 (16%) fell below the line (Appendix II) and, of those 10 points, only three were without extenuating circumstances. With the "exception" of these cases, no patient whose plot was initially within the minimum risk zone and remained within the minimum risk zone during the study period developed any form of clinical ASD to date.

Nineteen plots fell close to the threshold line. Four were men aged 72-79 years; and three have died. The other three male plots were those of a 67 year-old man, a 44 year-old man with a positive treadmill test, and a 55 year-old man who died suddenly. Of the 12 female plots, three involved cases in which LDL levels exceeded 170 mg/dl cut-off, above which HDL is no longer able to compensate for LDL. Of the other nine plots, one involved a 74 year-old woman who had much higher lipids in the past in association with a severe untreated hypothyroid condition. The thyroid abnormality was corrected, and her plot represented her lipids after she achieved the euthyroid state. The other female plots mainly represented women in their seventies. Only three of the twelve women have died.

The value of the BGS Graphs in guiding therapy has been demonstrated by evidence that only one asymptomatic patient initially in the danger zone suffered subsequent clinical ASD after being brought into the minimum risk zone and maintained there for a minimum of two years. The one exception was a 62 year-old woman who had a previous history of hypertension, but had discontinued her medication prior to her initial visit. Initial blood

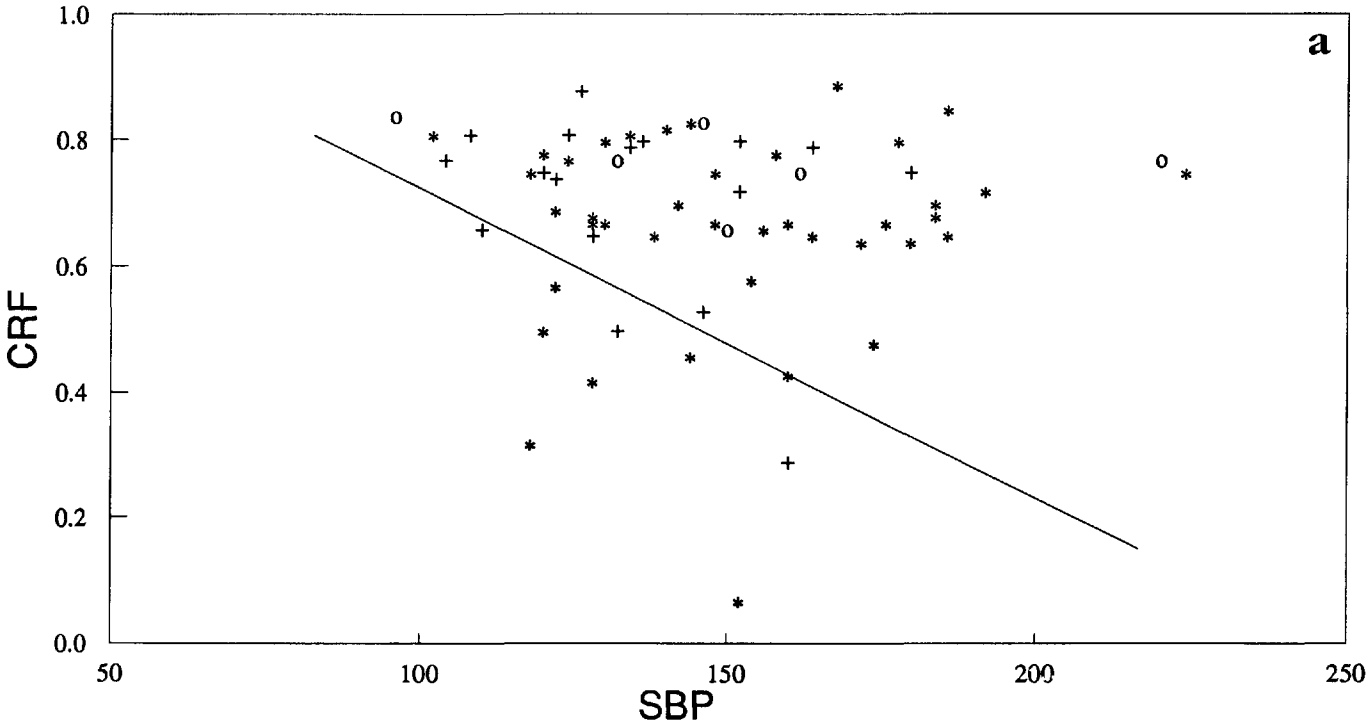


FIGURE 1. Relationship between cholesterol retention fraction (CRF) and systolic blood pressure (SBP) in subjects who suffered any form of clinical atherosclerotic disease (ASD), from 4 November 1974 – 1 January 1991. a) Subjects who had never smoked cigarettes. b) Smokers who had stopped using cigarettes at least six month prior to the initial ASD event. c) Current smokers, or subjects who had stopped using cigarettes less than six month prior to ASD.

*Female subjects.
+Male subjects.
⁰Male subjects in a) who used alternate tobacco products (chewing tobacco, pipe, cigar).

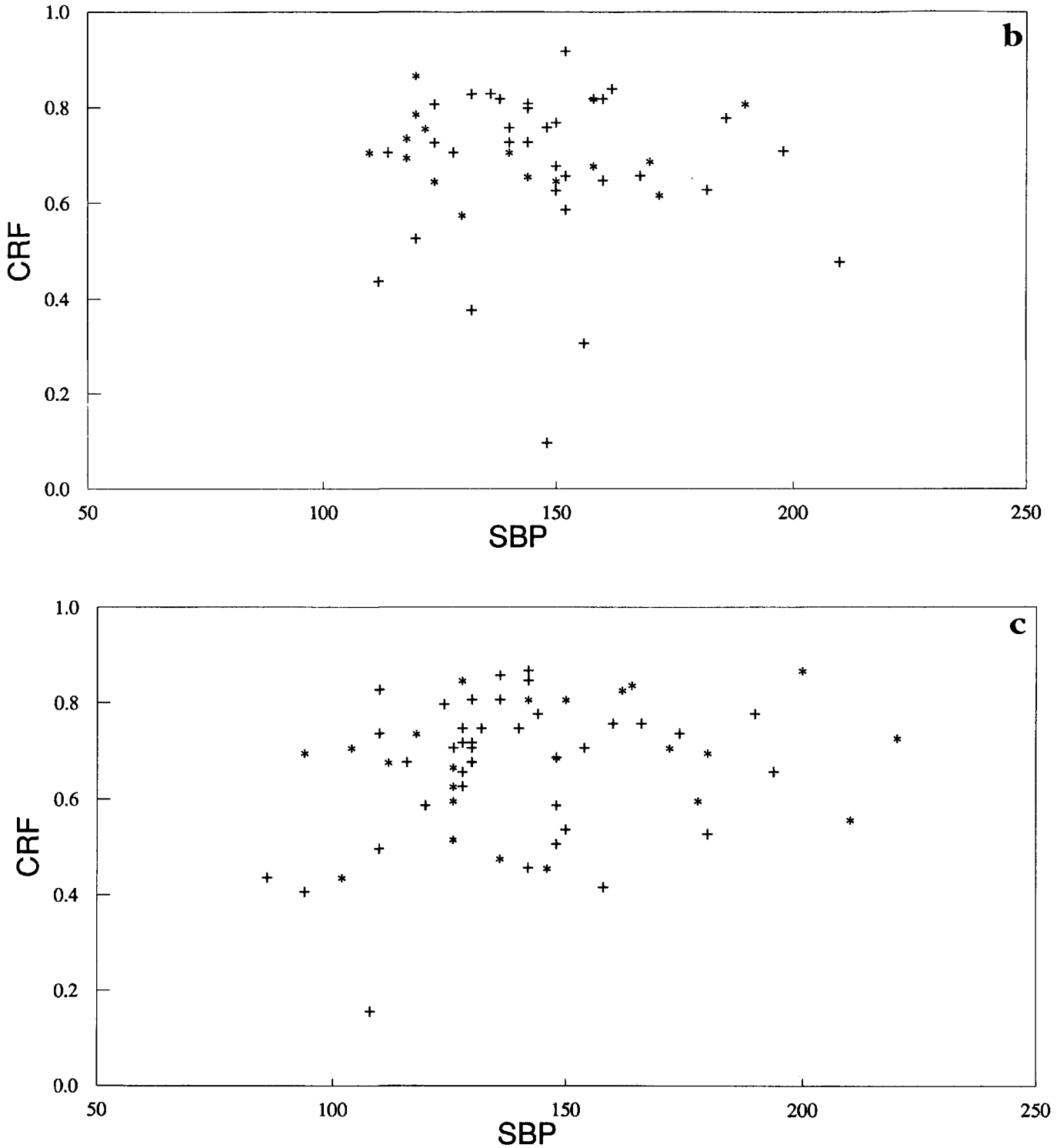


FIGURE 1. (Continued)

pressure and lipid chemistry in 1975 placed her deep in the danger zone and intervention was instituted to place her in the minimum risk zone. After ten years of treatment, she was found to have a severe asymptomatic carotid stenosis, which was surgically removed and has not recurred. She also developed a mild case of angina pectoris, which resolved on aspirin therapy.

Changes in C_T might also predict ASD resolution. However, C_T was not a good predictor of the cholesterol portion of ASD risk (Figs. 2, 3). Distribution curves comparing C_T values in people with and without ASD for both male (Fig. 2a) and female (Fig. 2b) patients were biphasic, with a peak at lower C_T levels and another peak at higher C_T levels. The lower peak represented HDL disease whereas the higher peak represented LDL disease. Curves for the age at ASD onset in men and women, as a function of C_T, were likewise not continuous, but rather appeared to represent two distinct populations, one for LDL disease and one for HDL disease (Fig. 3). Moreover, the "uppermost" end of each curve portion began at about

the same age, indicating that LDL disease and HDL disease are almost equipotent in causing ASD. Whereas LDL abnormalities could be detected by C_T screening, HDL abnormalities would be missed since low levels of HDL do not result in high levels of C_T.

These graphic representations (Figs. 2, 3) were based on C_T alone and did not take into account cigarette smoking. The pertinence of stratifying cholesterol risk in terms of cigarette smoking was ascertained (Fig. 4a,b). This approach demonstrated that in the absence of cigarette smoking, there was a direct relationship between the CRF and the age at ASD onset, whereas cigarette smoking eliminated the relationship. The relation between CRF and smoking for ex-smokers was intermediate. However, examination of this relationship in terms of C_T revealed that even in the absence of cigarette smoking, C_T did not provide a smooth predictor of ASD risk (Fig. 5a,b). A graph constructed using C_T on the ordinate and SBP on the abscissa showed no predictive pattern, and indeed resembled a random scattering of plots.

Dyslipidemia and Hypertension

The link between dyslipidemia (DLP) and hypertension (HT) has been examined in the present study. Since 1974, the BGS has evaluated 177 men and women who were found to have incidental HT. It has been the policy of this study that all patients over one year old will have BP taken at each office visit, regardless of the nature of the presenting complaint. If SBP was 140 mm HG or higher, the patient was asked to return weekly for four weeks to have his/her BP taken. If the BP remained high on these repeat measurements, lipids were tested. To be eligible for this substudy, the patient could have not had any other compelling reason for lipid testing such as chest pain, diabetes, a family history of ASD, a family history of DLP, and so on.

From 1 January 1978 (when LDL and HDL testing became available to the BGS) to 1 January 1991, the BGS has accumulated complete lipid data on 67 men and 56 women with incidental HT. Of that population, 58% of men and 47% of women had cholesterol abnormalities exceeding C Thr (CRF $\geq$ 0.70 or LDL $\geq$ 170 mg/dl). An additional four men (6%) and two women (3%) had borderline CRF values of 0.68 or 0.69. Given this intimate association between DLP and HT, it would appear to be unwise for a treating physician to use antihypertensive medications that adversely effect the lipids.

Evidence supporting this proposition can be found by examining the average ages of ASD onset in terms of dyslipidemic vs. normolipidemic hypertension. If one ignores the cigarette-smoking status of ASD patients, then of the 59 male and 65 female hypertensive ASD patients, 36 males (61%) and 31 females (48%) were dyslipidemic (exceeded C Thr). The dyslipidemic hypertensive male ASD patients had an average age of ASD onset of 66 years and 39% have died. Comparatively, the 23 normolipidemic

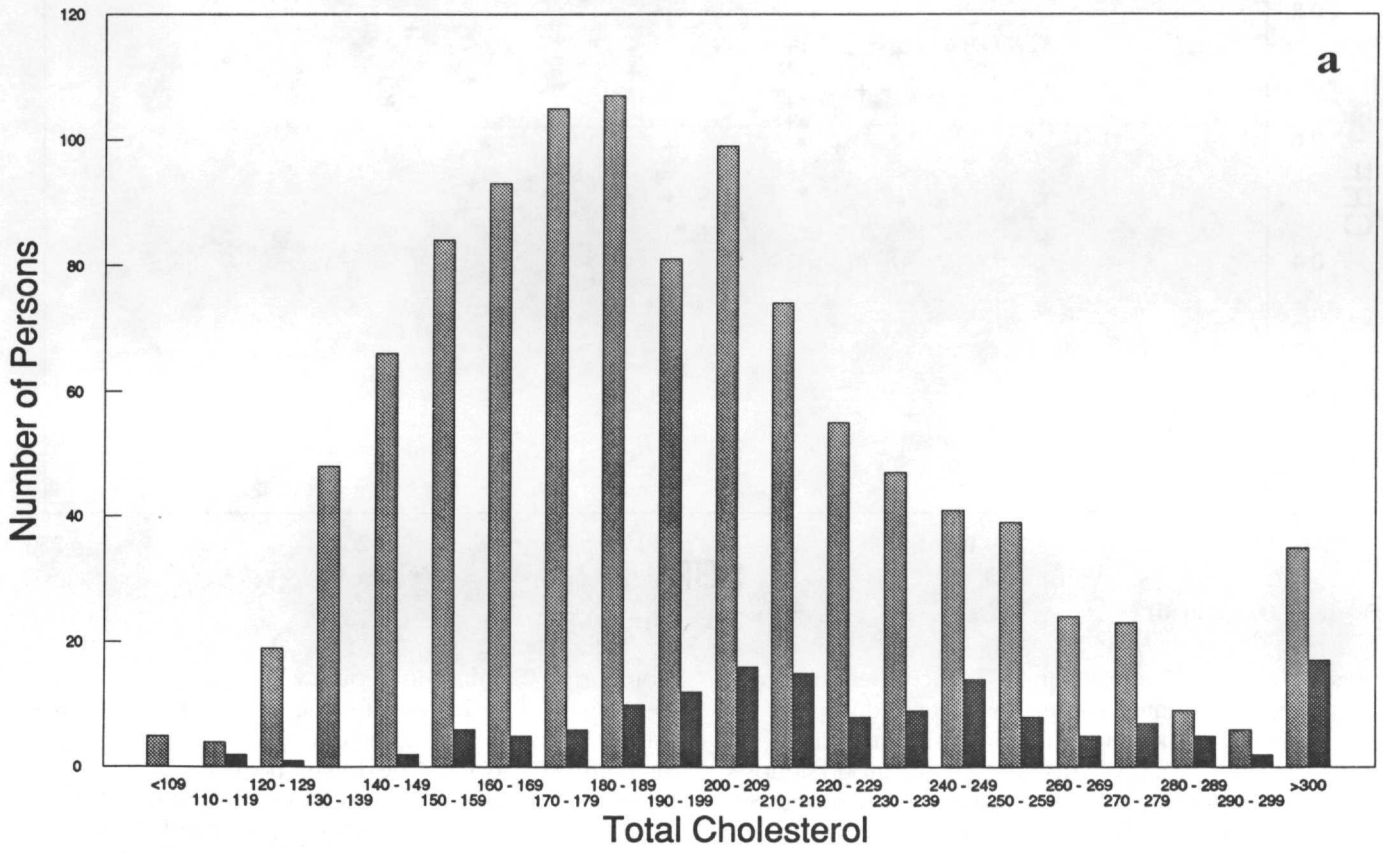
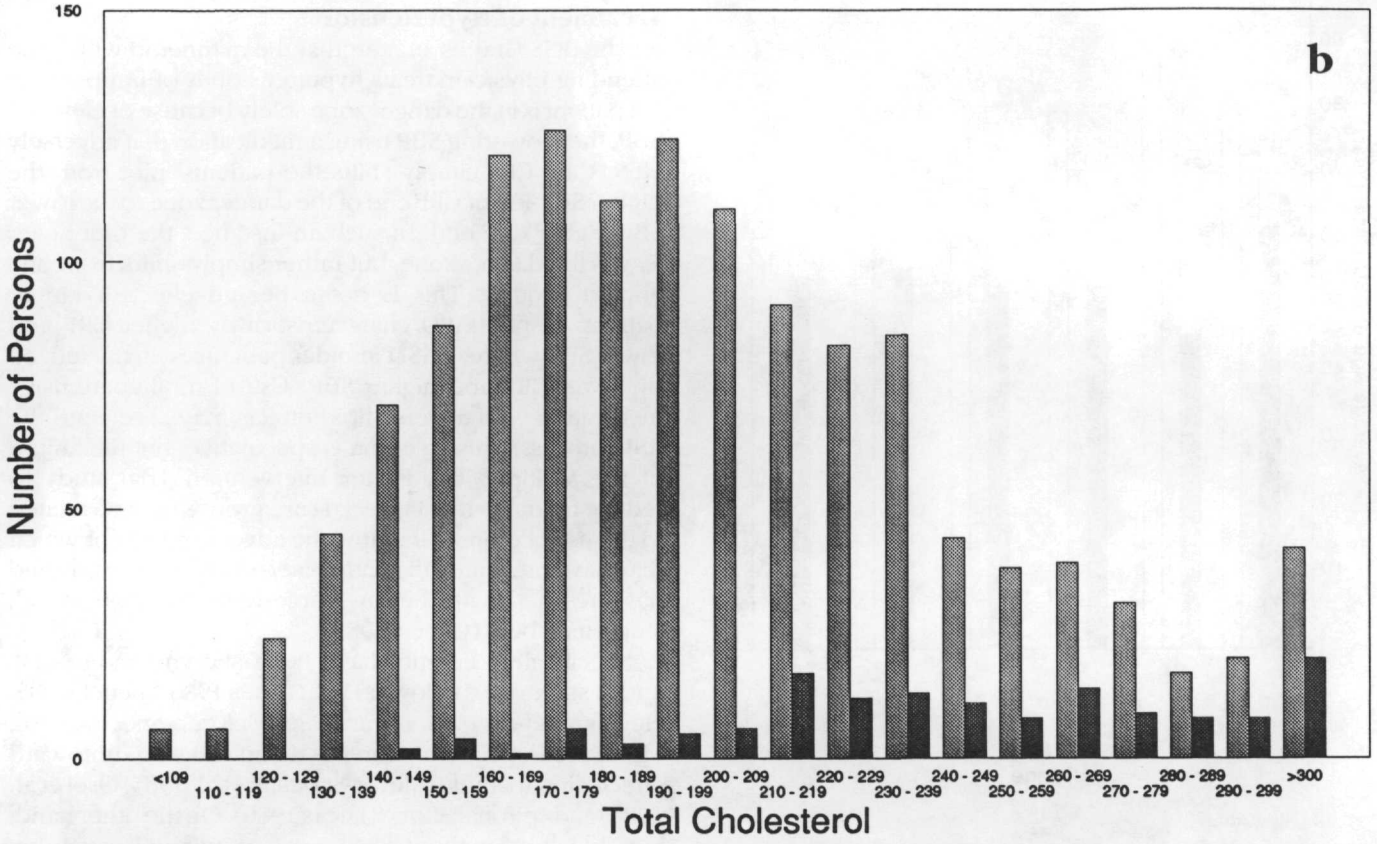


FIGURE 2. Frequency distribution of atherosclerotic disease (ASD) as compared with total serum cholesterol (mg/dl) in male (a) and female (b) patients.

Light bars = Patients not known to have developed ASD.
Dark bars = Patients known to have developed ASD.



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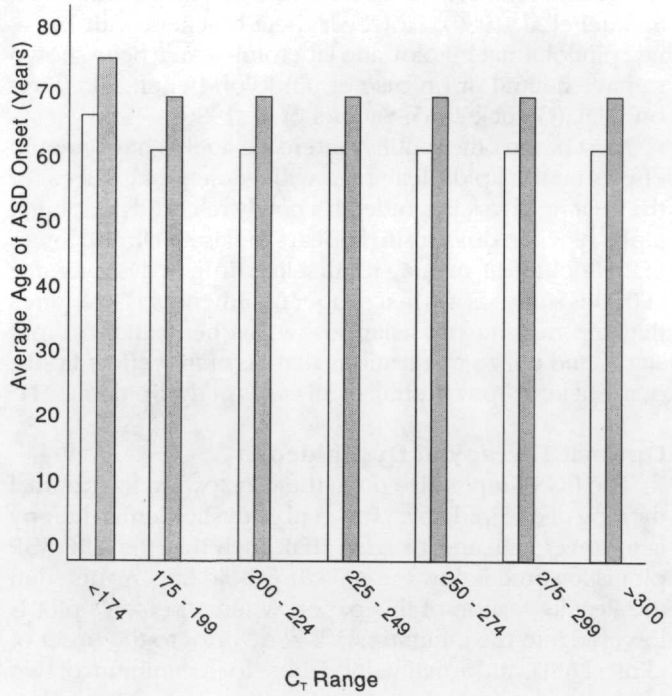

FIGURE 3. Average age of initial atherosclerotic disease event relative to total serum cholesterol cohort (mg/dl).

Light bars = Male patients.
Dark bars = Female patients.

hypertensive male ASD patients had an average age of ASD onset of 68 years and 22% have died. The dyslipidemic hypertensive female ASD patients had an average age of ASD onset of 68 years and 29% have died. Comparatively, the 34 normolipidemic hypertensive female ASD patients had an average age of ASD onset of 75 years and 26% have died. Thus, dyslipidemic hypertensive ASD patients have their ASD occurring earlier in life and that ASD is more likely to be fatal.

A pattern similar to that above was seen if only never-smokers were examined. Such an analysis was limited by relatively few male patients, since the BGS age-sex registry revealed that most male ASD patients were current or former cigarette smokers. Thus, there were only 19 hypertensive male ASD patients who never smoked cigarettes. Of these 19 hypertensive patients, 14 were dyslipidemic. The average age of ASD onset of these 14 dyslipidemic hypertensive male ASD patients was 71 years, as compared to 77 years for the 5 normolipidemic hypertensive male ASD patients. There were 57 hypertensive female ASD patients who never smoked cigarettes. Of these 57 patients, 27 were dyslipidemic. The average age of ASD onset of these 27 dyslipidemic hypertensive female patients was 72 years, compared to 77 years for the 30 normolipidemic hypertensive female ASD patients.

DISCUSSION

The BGS Graphs (Fig. 1a-c) are useful tools for defining at-risk population for ASD and for guiding therapy of major ASD risk factors. The BGS Graphs clearly demonstrate the advantages of smoking discontinuation. The size of the minimum risk zone increases by orders of magnitude by the simple expedient of stopping smoking (Fig. 1c vs. 1b).

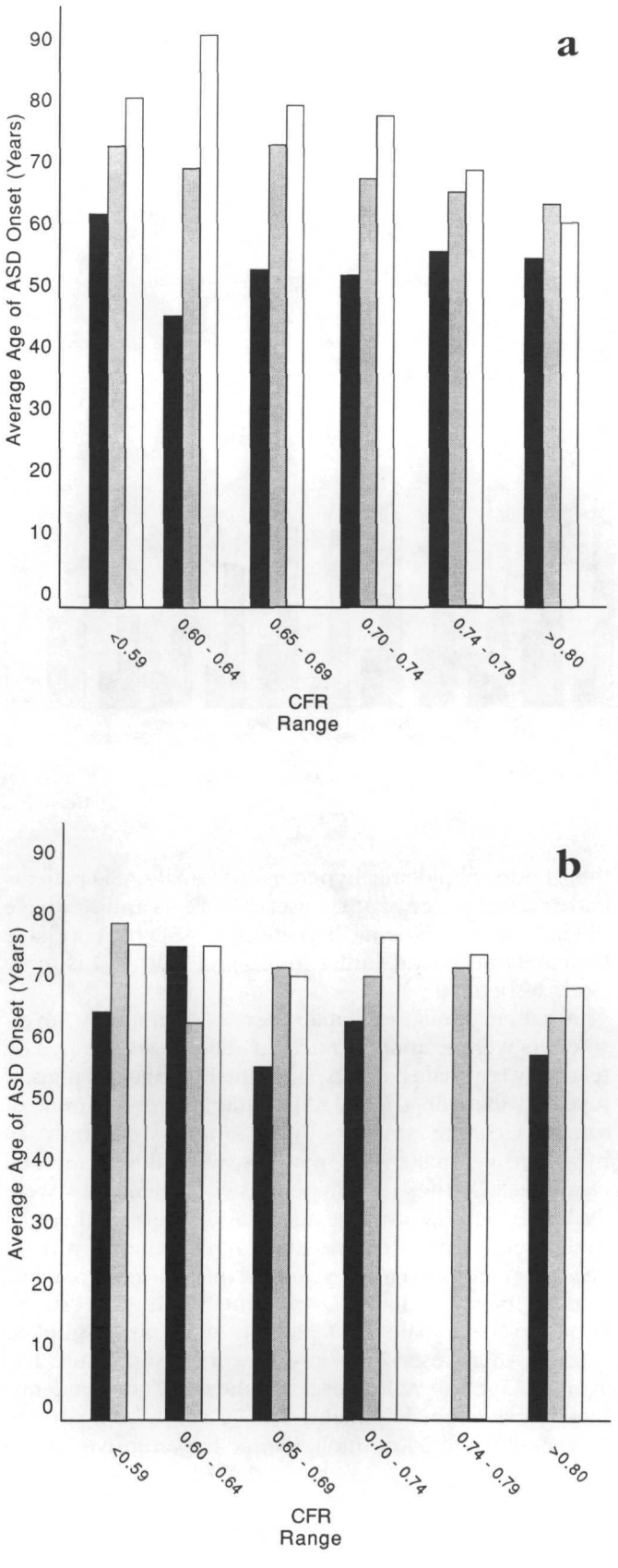

FIGURE 4. Average age of initial atherosclerotic disease (ASD) event relative to cholesterol retention fraction (CRF) cohort in men (a) and women (b) with different cigarette smoking status.

Open bars = Non-smokers.
Light bars = Past smokers.
Dark bars = Current smokers.

Treatment of Hypertension

The BGS Graphs suggest that the manner in which the attending physician treats hypertension is of importance. If a patient is in the danger zone solely because of elevated SBP, then lowering SBP using a medication that adversely effects the CRF simply shifts the patients' plot from the higher SBP-lower CRF end of the danger zone to the lower SBP-higher CRF end. In such an instance, the plot never leaves the danger zone, but rather simply shifts from one end to another. This is not a benign effect. Younger patients display ASD characteristics by higher CRF and lower SBP whereas ASD in older patients is characterized by lower CRF and higher SBP. Use of antihypertensive medication with adverse lipid effects may accelerate the ASD process. This assertion is speculative, but the failure of the Multiple Risk Factor Intervention Trial study to reduce mortality in the special care groups may be related to the use of diuretic therapy, the adverse effects of which may have prevented the anticipated drop in C_T that should have resulted with the low-cholesterol diet given to all study members (Cohen 1982).

Specifically, diuretics have been shown to raise LDL and in some cases to lower HDL (Ames 1986, Gleuck 1985, Hegeland et al. 1978, Lucas 1986, McKenney et al. 1986, Morin 1984). Only two diuretics do not have this untoward effect—indapamide (Meyer-Sabellak et al. 1985, Osei et al. 1986) and spironalactone (Lucas 1986). On the other hand, beta-blockers without ISA—i.e., propanolol, atenolol, metoprolol, etc.—have been shown to lower HDL (Hegeland et al. 1978, Hooper et al. 1981, Leren et al. 1980, Samuel et al. 1986). However, beta-blockers with ISA—i.e., pindolol, acebutolol, and labetolol—have been shown to have neutral or (in case of pindolol) beneficial effects on HDL (Gleuck 1985, Samuel et al. 1986).

Most of the other antihypertensive agents have neutral effects on the lipids, leaving a wide variety of choices for the treating physician. Indeed, a newly released peripheral alpha blocker, doxazosin, appears to raise HDL and lower LDL (Pool 1991), making it a first line drug in dyslipidemic HT. This study shows that proper treatment of HT requires that the treating physician know his/her patient's lipid status and utilize medications that favorably effect lipids, or are at least lipid neutral, in all cases of dyslipidemic HT.

Optimal Therapy of Dyslipidemia

The BGS Graphs also point the way toward the optimal therapy of dyslipidemia. The goal of dyslipidemic therapy is to lower LDL and/or raise HDL such that the CRF-SBP plot is lowered below the ASD threshold line. As noted in the Results section of this paper, when a person's plot is lowered into the minimum risk zone prior to the onset of clinical ASD, and is maintained there for a minimum of two years, then with one exception, no such person has developed clinical ASD. The patient who did develop ASD despite therapy that moved her plot into the minimum risk zone was 73 years old at the time of ASD onset, has suffered no major sequela except a carotid endarterectomy, and continues to lead an active life at 79 years of age.

The results of 15 international trials are presented (Appendix III). These trials can be stratified in terms of the CRF achieved during the trial and the consequent effect on

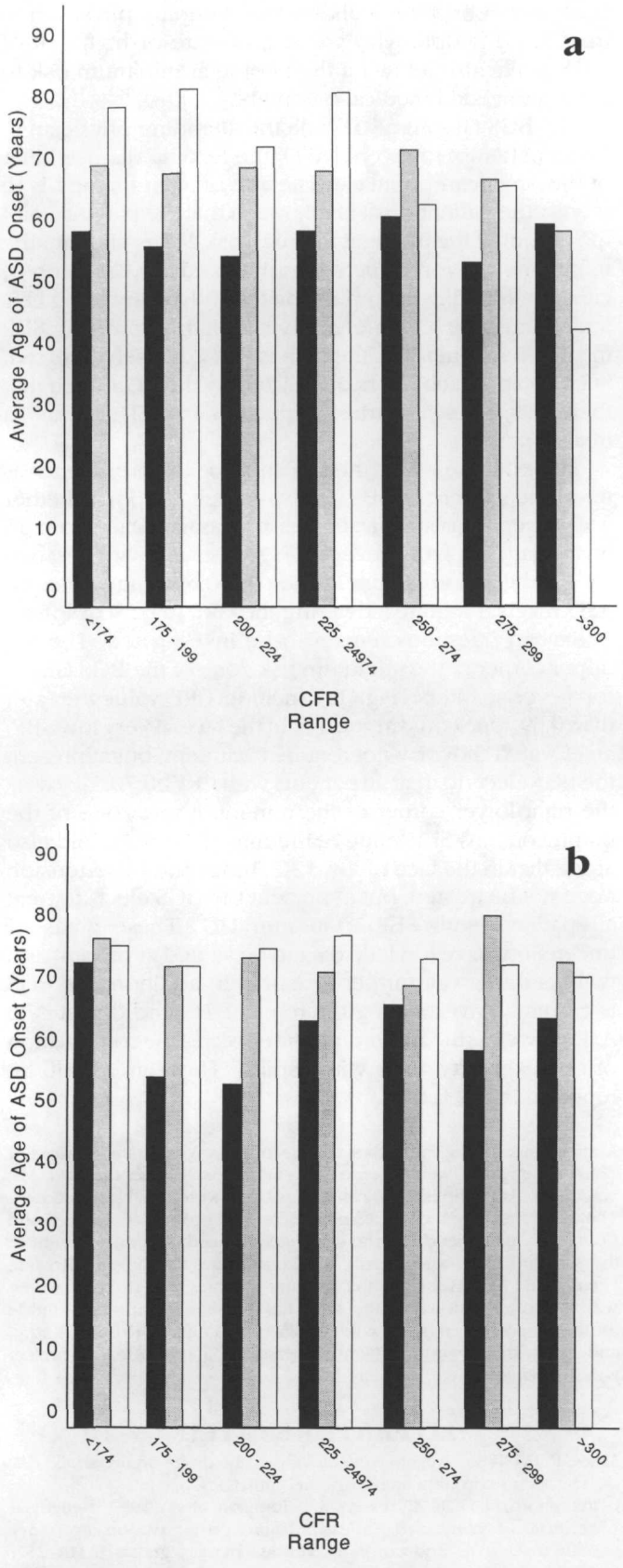

FIGURE 5. Average age of initial atherosclerotic disease (ASD) event relative to total serum cholesterol (C_T, mg/dl) cohort in men (a) and women (b) with different cigarette smoking status.

Open bars = Non-smokers.
Light bars = Past smokers.
Dark bars = Current smokers.

ASD (Fig. 6). It will be noted that the better the improvement in the CRF, the more likely ASD is to regress in follow-up evaluation. It is also true the better the improvement in the CRF, the faster plaque resolution occurs. The evidence for this proposition lies in the fact that in the LRC (Lipid Research Clinics 1984), in the HSS (Frick et al. 1987), and in the Buchwald group (Buchwald et al. 1990), improvement in subsequent ASHD morbidity in the treatment group was not evident until the third year of the study. However, in the Brown III group (Brown et al. 1990), angiographic regression was seen within 2.5 years and in the Blankenhorn study (Blankenhorn et al. 1987) significant plaque regression was noted within two years. The difference in time frame relates directly to the reduction in CRF obtained by the studies: 73% for the LRC, 71% for the HSS, 63% in the Buchwald group, 57% in the Brown III, and 37% for the Blankenhorn study. In addition, the LRC (CRF = 73%) reduced subsequent coronary events by 19% whereas the HSS (CRF = 71%) reduced subsequent coronary events by 34%.

Hypolipidemic Therapy

Once the C Thr is determined to be abnormal, the physician next determines which portion of the C Thr is responsible. In the BGS, the highest acceptable LDL is 169 mg/dl (4.4 mmoles/L) and the lowest acceptable HDL is 40 mg/dl (1.0 mmole/L). It should be noted that different laboratories use different techniques to measure the various lipid fractions; hence, the upper and lower limits of normal for these fractions will vary from lab to lab. The values presented here represent those values obtained by the BGS regional reference lab in Toledo, OH, and should be used by physicians active in the fight against ASD as guidelines until such time individual physicians can establish their own guidelines by examining their own patient population. Such "new" guidelines should not differ much from the BGS standards.

If the LDL is at fault or predominantly at fault, a therapeutic regimen aimed at reducing LDL should be initiated. Such a regimen begins with a diet low in saturated fat and cholesterol. If obesity is present, weight loss is recommended. In the experience of the BGS, diet is often not effective in reducing LDL to the requisite 169 mg/dl or less. At this point a LDL drug should be used (Table 12). The BGS experience with the various LDL drugs is discussed (Appendix IV).

On the other hand, if the CRF is abnormal because of HDL, then an HDL regimen is used. Such a regimen cannot include an LDL diet unless LDL is also elevated because a low cholesterol, low saturated fat diet is also a cause of low HDL levels (Miettenen 1982). Indeed, the philosophy of the present study is to correct an HDL defect if such exists rather than to use an LDL regimen where no disorder of LDL is evident. The initial step, then, is to do those things that are known to elevate HDL. The BGS first prescribes an exercise program (Eder 1981) and, if no personal or family history of alcoholism is present, a minimal intake of ethanol of one ounce per day (Criqui 1986) is prescribed. If obesity is present, weight control is advised (Hartung 1983). Smoking is always proscribed as it accelerates the course of ASD, especially in patients with low HDL (BGS

unpublished data). If patients are unwilling or unable to comply with this regimen, then an HDL drug is utilized (Table 12, Appendix IV). The goal of this therapy is to raise HDL such that the CRF is brought below 0.69. The BGS experience with HDL drugs is discussed (Appendix IV).

Finally, if both LDL and HDL abnormalities are present, a combined approach is used. Such a regimen includes low saturated fat/cholesterol diet, exercise, weight loss, and smoking cessation. If this regimen fails to bring the cholesterol level below the C Thr, various combinations of LDL and HDL medications are employed to achieve this goal.

The goal of these two regimens is to retard the ASD process by correcting the lipid fraction responsible. This is achieved by lowering LDL below 170 mg/dl (4.4 mmoles/L) and raising HDL above 40 mg/dl (1.0 mmole/L), such that the CRF is maintained below 70% in patients free of clinical ASD, and below 60% in patients with clinical ASD. The rationale for these goals is demonstrated by the ASD plaque dynamics at various levels of CRF (Fig. 6).

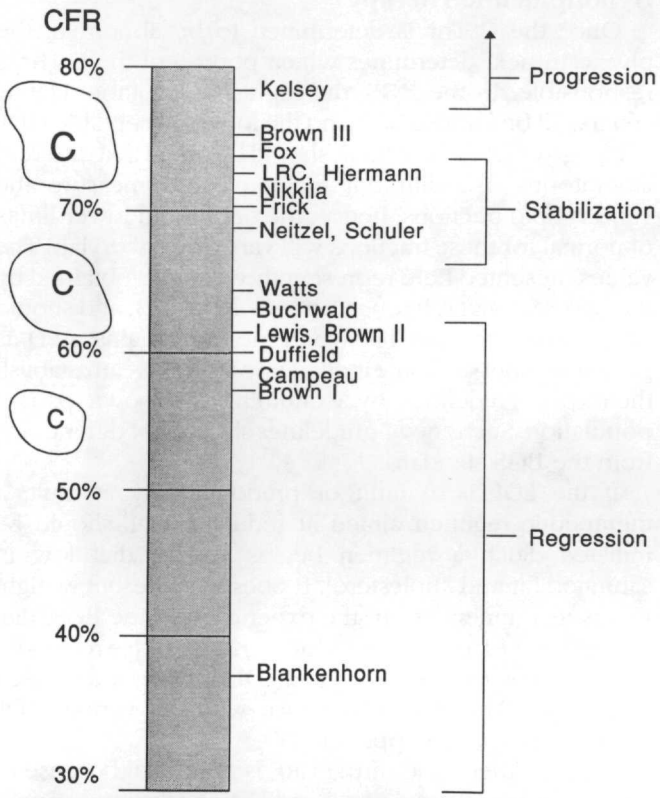

FIGURE 6. Comparison of cholesterol retention fraction (CRF) with results noted during studies of atherosclerotic disease (ASD): regression, stabilization, or progression of plaques. Names refer to authors of papers reporting results. Size of "circle" enclosing the C in the CRF column represents the amount of cholesterol remaining in the arterial wall.

CONCLUSIONS

The BGS has evolved a series of graphs (Fig. 1) that define at a single pass the population at risk for ASD. These graphs combine the three major risk factors for ASD: CRF, cigarette smoking, and hypertension. By defining the population at risk of ASD, the BGS Graphs simultaneously define the population at minimal risk. Such a distinction is important because it allows the attending physician to treat those people who are at moderate or high risk of ASD, while also allowing the people at minimum risk to avoid unneeded medical treatment.

The BGS Graphs also guide the attending physician in his/her attempt to reverse ASD, the leading disease killer of the American populace. The aim of such therapy is to modify the patient's risk factors such that the patient's plot moves out of the moderate or high risk zones and into the minimum risk zone. Such therapy mandates cessation of cigarette smoking, manipulating the CRF by lowering LDL and/or raising HDL (preferably both), and lowering SBP in such a manner that the CRF is not adversely affected. Such an approach has been utilized by the BGS, such that there has been a marked reduction in ASD events in treated patients.

The extent to which the CRF must be lowered depends upon the associated SBP. It also depends upon whether ASD reversal or stabilization is necessary. Data from 15 investigations of ASD reversal (Fig. 6) strongly suggest that ASD stabilization occurs in the 0.60-0.69 range whereas ASD reversal requires lowering the CRF to 0.59 or lower.

Several questions remain to be investigated. The left upper corner of the minimum risk zone of the BGS Graph for never-smokers (Fig. 1a) include CRF values greater than 0.69. One could argue that in the face of very low SBP, an elevated CRF may not require treatment, but at present the BGS elects to treat all patients with CRF ≥0.70. Likewise the right lower corner of the minimum risk zone of the graph contains SBP values ≥140 mm HG. One could also argue that in the face of low CRF, moderate hypertension need not be treated, but at present the BGS elects to treat all patients with SBP ≥140 mm HG. These areas of uncertainty have too little data to be settled at present and will need to await further research. In addition, the BGS is currently investigating the roles of TG and diabetes in ASD, as well as the antithrombotic effects of the combination of omega-3 fatty acids with aspirin. These areas will be reported in the future.

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LITERATURE CITED

Ames, R. P. 1986 Negative effects of diuretic drugs on metabolic risk factors for coronary artery disease. mmHG 5: 6.

Blankenhorn, D. H., S. A. Nessim, R. L. Johnson, et al. 1987 Beneficial effects of combined Colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. JAMA 257: 3233-3240.

Brown, G., J. J. Albers, L. D. Fisher, et al. 1990 Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apoliprotein B. New Engl. J. Med. 323: 1289-1298.

Buchwald, H., R. L. Varco, J. P. Matts, et al. 1990 Effect of partial ileus bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesteremia. New Engl. J. Med. 323: 946-955.

Campeau, L., M. Enjalbert, J. Lesperance, et al. 1984 The relation of risk factors to the development of atherosclerosis in saphenous-vein bypass grafts and the progression of disease in the native circulation. New Engl. J. Med. 311: 1329-1332.

Cohen, J. D. 1982 Four-year hypertension treatment results and effects on serum cholesterol and cigarette smoking. Primary Cardiology 311: 109-121.

Criqui, M. H. 1986 Epidemiology of atherosclerosis: An updated overview. Am. J. Cardiol. 57: 18C-23C.

Duffield, R. G. M., B. Lewis, N. E. Miller, et al. 1983 Treatment of hyperlipidemia retards progression of symptomatic femoral atherosclerosis: A randomized controlled trial. Lancet 2: 639-642.

Eder, H. A. 1981 Hyperlipidemia: A Cornell postgraduate course. Medcom, Inc., New York. pp. 21-26.

Fox, M. H., H. W. Gruchow, J. J. Barboriak, et al. 1987 Risk factors among patients undergoing repeat aorta coronary bypass procedures. S. Thoracic Cardiovasc. Surg. 93: 56-61.

Fraelecher, V. F. 1973 Dietary prevention of atherosclerosis. Amer. Family Physician 7: 79-85.

Frick, M. H., D. Elo, K. Harpa, et al. 1987 Helsinki heart study: Primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. New Engl. J. Med. 317: 1237-1245.

Glueck, C. J. 1985 Nonpharmologic and pharmologic alteration of high-density lipoprotein cholesterol: Therapuetic approaches to prevention of atherosclerosis. Am. Heart J. 110: 1107-1115.

Hartung, G. H. 1983 Environmental and dietary influences on the HDL/LDL cholesterol ratio. Practical Cardiology 9: 61-68.

Havel, R. J., D. B. Hunninghake, D. R. Illingworth, et al. 1987 Lovastatin (Mevolin) in the treatment of heterozygous familial hypercholesterolemia: A multicenter study. Ann. Intern Med. 107: 609-615.

Heart Facts 1988 American Heart Association. p. 1.

Hegeland, A., I. Hjerman, P. Leren, et al. 1978 High density lipoprotein cholesterol and antihypertensive drugs. Brit. Med. J. 2: 403.

Hirvonen, E., M. Maikonen, and V. Manninen 1981 Effects of different progesterogens on lipoprotein during postmenopausal replacement therapy. New Engl. J. Med. 304: 560-563.

Hjerman, I., I. Holme, P. Leren 1986 Oslo study diet and antismoking trial: Results after 102 months. Am. J. Med. 80(2A): 7-11.

Hooper, P. C., W. Woo, L. Vosconti, and D. Pathak 1981 Terbutaline raises high-density lipoprotein-cholesterol levels. New Engl. J. Med. 305: 1455-1467.

Kannel, W. B., M. J. Garcia, P. M. McNamara 1971 Serum lipid precursors of coronary heart disease. Hum. Pathol. 1: 129-151.

Kelsey, S. F. 1986 Progression of coronary artery disease. Primary Cardiology. pp. 77-87.

Kita, T., Y. Nagano, M. Yokode 1987 Probucol prevents the progression of atherosclerosis in Watanabe heritable hyperlipidemic rabbit, an animal model for familial hypercholesterolemia. Proc. Natl. Acad. Sci. USA 84: 5928-5931.

Leren, P., A. Hegeland, I. Holme, et al. 1980 Effect of Propanolol and Prasozin on blood lipids. Lancet 2: 4-6.

Levy, R. I. 1984 Hyperlipoproteinemia in coronary artery disease in the clinical significance of hyperlipidemia. Audiovisual Medical Marketing. pp. 11-13.

Lewis, B. 1985 Randomized controlled trial of the treatment of hyperlipidemia on progression of atherosclerosis. Acta. Med. Scand. [suppl] 701: 53-57.

Lipid Research Clinics 1984 The lipid research clinics coronary primary prevention trial results. JAMA 251: 351-374.

Lucas, C. P. 1986 The effects of antihypertensive agents on serum lipids and lipoproteins. Pract. Cardiol. [suppl]. pp. 55-64.

McKenney, J. M., R. P. Goodman, J. T. Wright, Jr., et al. 1986 The effect of low-dose hydrochlorothazide on blood pressure, serum potassium and lipoproteins. Pharmocotherapy 6: 179-184.

Meyer-Sabellak, W., R. Gotzen, J. Heitz, et al. 1985 Serum lipoprotein levels during long-term treatment of hypertension with Indapamide. Hypertension 7 [suppl] II: 170-174.

Miettenen, T. 1982 Is it harmful to lower HDL levels? JAMA 246: 2311-2315.

Miller, N. E. and T. Miller 1975 Plasma-high-density-lipoproteinemia and development of ischemic heart disease. Lancet 1: 16-19.

Morin, R. J. 1984 Atherosclerosis. Geriatric Consultant (Nov-Dec). pp. 11-17.

Neitzel, G. F., J. J. Barborial, K. Pintar, et al. 1986 Atherosclerosis in aorta-coronary bypass grafts morphologic study and risk factor analysis 6 to 12 years after surgery. Arteriosclerosis 6: 594-600.

Nikkila, E. A., P. Viikinkoski, M. Valle, and M. H. Frick 1984 Prevention of progression of coronary atherosclerosis by treatment of hyperlipidemia: A seven-year prospective angiographic study. Brit. Med. J. 289: 220-223.

Oliver, M. F. 1973 Report on ischemic heart disease in young women. JAMA 223: 1441.

Osei, K., G. Holland, and J. M. Galko 1986 Indapamide: Effects on apoprotein, lipoprotein, and glucoregulation in ambulatory diabetic patients. Arch. Intern. Med. 46: 1973-1977.

Pool, S. C. 1991 Effects of Doxazosin on serum lipids: A review of the clinical data and molecular basis for altered lipid metabolism. Am. Heart J. 121: 251-260.

Samuel, P. 1986 Conclusions. Amer. J. Cardiol. 57: 69C.

_____, B. Chin, R. W. Fenderson, et al. 1986 Improvement of the lipid profile during long-term administration of Pindolol and Hydrochlorothiazide in patients with hypertension. Am. J. Cardiol. 57: 24C-28C.

Schuler, G., G. Schlierf, A. Wirth, et al. 1988 Low-fat diet and regular supervised physical exercize in patients with symptomatic coronary artery disease: Reduction of stress-induced myocardial ischemia. Circ. 77: 172-181.

Shepherd, J., C. Packard, J. R. Patsch, et al. 1979 Effects of nicotinic acid therapy on plasma high-density lipoprotein supfraction distribution and composition and on apoprotein A metabolism. J. Clin. Invest. 63: 858-867.

_____, C. J. Packard, S. Bicker, et al. 1980 Cholestyramine promotes receptor-mediated low-density-lipoprotein catabolism. New Engl. J. Med. 302: 1219-1222.

Steinberg, D. 1986 Studies on the mechanism of action of Probucol. Am. J. Cardiol. 57: 16H-21H.

Tikkanen, M. J., E. A. Nikkila, and E. Vartiaren 1978 Natural oesterogen as an effective treatment for type II hyperlipoproteinemia in postmenopausal women. Lancet 2: 490-491.

Vega, G. L. and S. M. Grundy 1985 Gemfibrozil therapy in primary hypertriglyceridemia associated with coronary heart disease: Effects on metabolism of low-density lipoproteins. JAMA 253: 2398-2403.

Watts, G. F., N. Lewis, J. N. H. Brunt, et al. 1992 Effects on coronary artery disease of lipid-lowering diet or diet plus cholestyramine in the St. Thomas atherosclerosis regression study (STARS). Lancet 339: 563-569.

APPENDIX I

Appendix I lists all BGS patients who developed some form of clinical ASD from 4 November 1974 to 1 January 1991. As of 1 January 1991, 196 men and 195 women sustained some form of clinical ASD, giving a prevalence rate of 4.8 per 100 men and 4.4 per 100 women. One hundred sixty-five men and 167 women suffered some manifestation of ASD of the heart (ASHD); 60 men and 55 women suffered some manifestation of ASD of the cerebral circulation (ASBD); and 39 men and 24 women suffered some manifestation of ASD of the peripheral vasculature (ASVD). A description of the criteria used to diagnose each of the individual ASD categories follows:

1) Acute Myocardial Infarction (AMI): Typical midsternal chest pain described as a heavy weight/pressure sensation, as a gripping/squeezing sensation, or sometimes as an ache, accompanied by typical EKG and/or cardiac enzyme changes. Radiation to the left arm or to the jaws, though often present, was not required for this diagnosis.

2) Angina Pectoris (AP): Typical midsternal chest pain, usually described as above, but not in an acute setting and not accompanied by the typical EKG changes and/or enzyme changes. Such pain was usually precipitated by exertion or emotion, and less commonly by exposure to the cold or by eating. Treadmill tests were used to verify the diagnosis; a positive test was required to make the diagnosis. From time to time, an anginal equivalent symptom such as shortness of breath or dizziness was accepted in lieu of chest pain, and in such cases a positive treadmill test was also required to make this diagnosis. Relief of pain with rest and/or nitroglycerin was also required to support the diagnosis.

3) Acute Coronary Insufficiency (ACI): Typical pain as described above, in an acute setting, but without EKG and/or cardiac enzyme changes. These patients were generally stabilized at Wood County Hospital and transferred to Toledo for definitive care, which usually meant coronary artery bypass graft surgery.

Appendix (Continued)

4) History of ASHD (HX): This category includes various groups of patients, but chiefly those who have had an EKG showing an old AMI or those who have been diagnosed as having ASHD by a physician licensed to practice medicine in the state of Ohio, or occasionally in some other state. Where possible, the diagnosis was verified by review of the medical records.

5) Congestive Heart Failure (CHF): Shortness of breath and limitation of physical activity, accompanied by bilateral rales on auscultation of the lungs and/ or compatible chest radiographs. A therapeutic response to diuretics and digitalis was required to confirm the diagnosis.

6) Positive Treadmill/Coronary Angiogram: This category includes those patients with atypical symptoms, which nonetheless suggested ASHD, and in whom the treadmill test was read as positive by the Wood County internists or cardiologists, or in whom the coronary angiogram showed at least 50% luminal narrowing.

7) Hemorrhagic Stroke (CVA): One woman presented with acute headache, nuchal rigidity, and blood in spinal fluid. Her aneurysm was surgically treated in Toledo after stabilization in Wood County Hospital. The other woman presented in coma and had a CAT scan, which showed a hemorrhagic stroke.

8) Thrombotic Stroke (TCVA): Acute onset of unilateral weakness or paralysis with or without accompanying paresthesis. These symptoms could be definite or progressive; however, they had to persist over a time. Progressive symptoms were treated with heparin and usually resolved with protracted span of anticoagulation. Patients with nonatherogenic sources of cerebral emboli, such as rheumatic heart disease, were excluded from this category.

9) Transient Ischemic Attack (TIA): Symptoms as above, but of a transient nature, resolving spontaneously within an hour.

10) Asymptomatic Carotid Stenosis (ACS): Findings of an asymptomatic carotid bruit on routine physical examination with confirmation by doppler. If the doppler suggested more than 50% stenosis, angiographic studies were done to confirm the diagnosis, but for more severe cases surgical confirmation was accepted.

11) History of ASBD (HX): Diagnosis of an ASBD event was made by another physician licensed to practice medicine in the state of Ohio, with confirmation by review of medical records where possible. Also accepted in this category were the patients with CAT scans of the brain that showed old CVAs.

12) Thoracic Aortic Aneurysm (TAA): This diagnosis was made on chest x-ray in one case and at autopsy on the other case.

13) Abdominal Aortic Aneurysm (AAA): Findings of a large pulsating abdominal mass on examination of the abdomen, with confirmation by echo or CAT scan. AAA could also be an incidental finding on radiographic evaluation of the abdomen.

14) ASD of the arteries below the level of the aorta (ASPVD): Findings of cold, bluish feet usually without a palpable pulse on physical exam or history of intermittent claudication. An incidental finding of ASPVD during radiographic evaluation of other areas was also accepted.

15) History of ASPVD (HX): Diagnosis was made by another physician licensed to practice medicine in the state of Ohio; most patients had been previously operated on for AAA.

In these tables, the "age" column refers to the age at onset of ASD in ASHD, ASBD, or ASVD. The presence of "†" beside the age indicates that the patient has expired. A "•" before the designation in the ASHD column indicates that the patient has multisystem ASD. The "C_T, HDL, LDL, CRF, TG, and PSL" columns derive from screening tests done for many reasons, one of which could be ASD; however, such data was often obtained months to years prior to the actual onset of clinical ASD. The "Cigarettes" column refers to the patient's status regarding smoking at the time of his/her initial ASD event; a "+" means that he/she was smoking at the ASD onset, whereas a "past" means that he/she had quit smoking at least six months prior, and a "–" means that he/she never smoked cigarettes. Some men had smoked pipes or cigars, or had chewed tobacco, without ever having smoked a cigarette, and this is indicated with the appropriate label. The column labeled "PSL" refers to the 2 hr postprandial plasma sugar level. Where the data is not available, but where the patient is know to be diabetic, a "D" is used to designate this condition. A "D" is also used to designate a known diabetic whose PSL value is less than 200 mg/dl; in such cases the actual test value obtained has a "D" appended. The other physical parameters were obtained at the time of the patient's first visit to the author's office, usually months to years prior to the first clinical event. "IH" behind the datum means that inhospital values were used. "RX" behind the datum means that the parameter had already been treated by another physician. A "*" behind one woman's lipids (Table 9) indicates that these were the values after treatment of a severe untreated hypothyroid condition.

TABLE 6

Male ASHD.

Age	ASHD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
24	AP	209	33	134	0.75	211	90	+	138	76	22
33	AMI	217	48	148	0.68	105	74	+	116	70	25
34	AMI	248	47	163	0.71	192	93	+	154	96	33
35	AMI	319	60	204	0.71	273	74	past	114	74	27
36	AMI	334	33	265	0.88	178	102	–	126	80	28
39	HX	204	—	—	—	214	88	+	150	78	24
42	AMI	196IH	30IH	190IH	0.72	283IH	—	+	128	84	17
42	AMI	244	40	174	0.77	152	78	+	138	84	26
42	HX	389	27	338	0.92	118	95	past	152RX	80RX	40

TABLE 6 (Continued)

Age	ASHD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
43	AMI	278	—	—	—	78	95	–	178	84	20
43	AP	339IH	36IH	—	—	559IH	—	+	166	80	28
44	ACI	222	25	—	—	1168	449	+	130	80	29
44	+Treadmill	327	56	220	0.75	256	117	–	120RX	88RX	38
45	HX	248	—	—	—	250	75	+	124	60	24
45	AMI	214	26	140	0.81	242	—	+	130	88	26
45†	•SUD	188	34	92	0.63	310	—	+	128	78	27
45	HX	373	—	—	—	118	—	+	166	104	22
45	AP	258	32	168	0.81	288	104	–	124	86	34
45	HX	285	36	210	0.83	195	208	past	132	76	27
46	AP	186	—	—	—	264	102	past	210	120	37
46	AMI	258	—	—	—	168	125	+	132	74	26
46	HX	173	47	115	0.59	70	262	+	148	84	27
46	AMI	296	41	201	0.80	272	—	–	136	90	—
47	HX	279	32	200	0.84	235	69	past	162	108	22
47	ACI	239RX	25RX	173RX	0.86	206RX	—	+	136	84	37
47	HX	301	35	196	0.82	351	128	past	160	98	28
48	AP	212	—	—	—	278	152	+	168	84	29
48†	•HX	212	35	138	0.75	197D	—	+	132RX	72RX	28
48	•HX	173IH	54IH	92IH	0.41	133IH	—	+	94	66	15
49	AMI	275	—	—	—	140	117	+	140	68	24
49	HX	—	—	—	—	—	—	+	168	94	30
49	AMI	257	71	142	0.50	220	290	past pipe	132RX	86RX	35
50†	•HX	213	43	154	0.72	80	80	+	130	76	19
50	•AP	318	39	232	0.83	235	95	+	110	80	27
50	HX	274	66	195	0.66	81	—	+	194	106	21
51	AMI	—	—	—	—	—	—	+	124	90	—
51	HX	157	44	90	0.51	116	132	+	148RX	98RX	42
52†	•AP	304	—	—	—	360	181	+	190	104	39
52	ACI	194	30	138	0.78	130	93	+	144	80	30
52	HX	—	—	—	—	—	—	past	126RX	90RX	—
53	AMI	220	—	—	—	173	122	+	152	90	24
53	•AMI	247	—	—	—	614	607	past	118	78	29
53†	HX	—	—	—	—	—	—	+	168	98	30
53	AP	216	34	166	0.80	81	108	+	124	90	24
53	HX	216	33	162	0.80	104	103	–	152	90	26
53†	CHF	193	48	118	0.59	136	127	+	120	92	22
54†	SUD	212	—	—	—	299	101	+	150	94	33
54†	•AMI	270	—	—	—	263	136D	+	162	90	31

TABLE 6 (Continued)

Age	ASHD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
54	AMI	193	34	136	0.75	116	226	+	140	90	27
55	•AP	192	—	—	—	124	78	past	154	94	33
55†	SUD	269	40	153	0.74	381	99	–	122	78	30
56	•AP	246	51	162	0.69	167	99	+	148	92	26
56	AMI	230	—	—	—	206	113	+	132	98	24
56	•HX	—	—	—	—	—	—	+	142	100	22
57	AMI	213	50	107	0.53	278	100	+	180	100	28
57	+Treadmill	—	—	—	—	—	—	–	128	80	25
57	AP	188	64	111	0.42	77	184	+	158	100	28
57	HX	200	36	148	0.76	82	127	past	148	80	29
57	AMI	282	58	222	0.74	200	124	+	110	70	32
58	ACI	153	—	—	—	276	—	past	158	104	35
58	AMI	245	36	159	0.77	252	415	past	150	94	29
58	•HX	244	—	—	—	193	94	past	160RX	92RX	34
58	CHF	—	—	—	—	—	—	+	136	78	24
59	HX	206	—	—	—	161	64	+	140	72	23
59†	CHF	235	31	167	0.81	185	144	+	136	74	29
59	AP	256	—	—	—	258	110	–	142RX	110RX	31
59†	SUD	—	—	—	—	—	—	+	122	82	25
60†	AMI	200	—	—	—	166	93	+	184	120	31
60†	•AP	173	—	—	—	93	162D	pipe	162RX	84RX	24
60	HX	249	31	173	0.82	225	111	past	138	74	24
60	AMI	240	—	—	—	155	155	pipe	164	96	33
60	HX	203	34	142	0.76	136	89	+	160	98	36
60	HX	192	48	89	0.46	277	114	+	142	88	24
61	AMI	387	51	307	0.83	184	117	past	136	80	28
61	HX	224	24	159	0.85	207	100	+	142	88	26
62	AP	226	—	—	—	198	198	+	204	110	40
62	+Treadmill	235	40	139	0.71	278	127	+	126	78	24
62†	HX	—	—	—	—	—	—	+	128RX	80RX	28
63†	•AMI	261	—	—	—	105	115	past	158	90	27
63†	•AMI	214	—	—	—	150	93	pipe	154	84	28
63	HX	183	48	116	0.59	97	114	past	152	92	19
63†	+ANGIOGRAM	212	59	126	0.53	136	—	past	120RX	82RX	30
63†	•HX	—	—	—	—	—	—	–	148	102	—
63	+Treadmill	324	30	237	0.87	284	125	+	142	64	30
64	•ACI	240	38	160	0.76	212	114	past	140	70	25
64†	•CHF	356	—	—	—	278	225	+	180	100	27
64†	AMI	216	44	154	0.71	91	—	past	198	100	—

TABLE 6 (Continued)

Age	ASHD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
65	AMI	—	—	—	—	—	—	past	138	66	23
65†	•HX	230	25	—	—	917	388	past	168	106	37
66	AMI	—	—	—	—	—	—	–	130	84	21
66	•AP	207	35	153	0.77	93	107	–	104	48	30
66†	•HX	169IH	—	—	—	—	—	+	188	100	28
66†	•HX	264	42	190	0.78	160	103	+	190	98	31
66†	AMI	—	—	—	—	—	—	past	130	96	—
66†	•SUD	301	49	207	0.76	223	112	+	166	104	26
66	•HX	263	42	188	0.78	163	125	past	186RX	42RX	23
67	HX	—	—	—	—	—	—	past	160	88	25
67†	AMI	—	—	—	—	—	—	past	190RX	80RX	34
67	HX	—	—	—	—	—	—	–	94	66	26
67	HX	—	—	—	—	—	—	–	136	80	29
68	AMI	314	44	238	0.82	160	151	past	158	78	27
68†	•AMI	310	—	—	—	126	108	+	168	88	26
68	AP	332	—	—	—	1014	181	+	152RX	84RX	28
68	HX	178	42	113	0.63	117	—	past	182	100	41
68†	HX	157IH	50IH	90IH	0.44IH	87IH	—	+	86	44	17
68	HX	—	—	—	—	—	—	past	144RX	80RX	36
69†	HX	191	—	—	—	128	82	+	146	96	25
69†	•AMI	243	—	—	—	225	87	+	138	82	20
69†	•CHF	126	52	62	0.16	61	89	+	108	60	24
69	CHF	238	55	148	0.63	176	217	past	150RX	70RX	34
69	+Treadmill	208	42	130	0.68	180	164	past	150	74	32
70†	HX	166	—	—	—	125	121	past	150	90	25
70	•HX	354RX	—	—	—	278RX	90	past	122	80	26
70	HX	244IH	34IH	175IH	0.81	176IH	—	past	124	80	27
70†	HX	230	71	143	0.50	79	—	–	110	62	19
70†	HX	—	—	—	—	—	168	–	130RX	90RX	29
70	•HX	—	—	—	—	—	—	past	130RX	70RX	32
71†	AMI	201	44	129	0.66	138	108	past	152RX	90RX	26
71	HX	—	—	—	—	—	—	past	160	90	32
71	•HX	114IH	35IH	49IH	0.29IH	151IH	—	–	160RX	84RX	—
71†	HX	254	38	190	0.80	131	—	past	144RX	76RX	24
71†	HX	—	—	—	—	—	—	+	128	80	16
72	HX	183	32	129	0.75	111	92	+	122	70	22
72	+Treadmill	204	—	—	—	288	94	past	142	80	28
72†	•HX	256	49	186	0.74	103	—	+	174	78	29
72†	CHF	206	29	154	0.81	113	—	–	108	70	—

TABLE 6 (Continued)

Age	ASHD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
73†	•HX	283	40	160	0.75	407	403	cigars	162	104	30
73†	•AP	263	38	196	0.81	146	133	past	144	76	29
73	•HX	212	47	136	0.66	137	102	past	168RX	100RX	27
73†	•AMI	163	32	94	0.66	183	326	chews	150RX	80RX	32
73†	•HX	168RX	41RX	73RX	0.44	270RX	—	past	112RX	78RX	27
74†	•CHF	264	41	175	0.77	241	140	pipe	220	108	28
74	HX	292	47	222	0.79	116	97	–	164	100	25
74	•HX	184IH	25IH	110IH	0.77	244IH	—	pipe	132	76	33
74	AP	227	46	167	0.72	71	94	–	152RX	80RX	30
75	HX	288RX	118RX	157RX	0.25	67RX	—	–	120	70	22
76	•AP	151IH	31IH	88IH	0.65	177IH	—	past	160RX	86RX	24
76†	HX	208	36	135	0.73	184	115	past chews	124	84	26
76†	•HX	242IH	34IH	136IH	0.75	360IH	—	+	128RX	80RX	34
76†	•AP	252	47	171	0.73	169	198	past	140	80	—
77	HX	181	80	88	0.10	66	94	past	148	94	27
78†	•HX	271	44	201	0.78	130	—	past	186	100	28
78	•HX	270	33	194	0.83	216	266	chews	146	94	30
79	•HX	117	34	73	0.53	52	91	past cigars	146	80	25
79†	CHF	—	—	—	—	—	—	cigars	118	70	22
79	HX	226	44	164	0.73	115	153	past	144	80	24
79†	HX	—	—	—	—	—	—	–	140RX	80RX	—
79	•AMI	178RX	37RX	124RX	0.70	86RX	—	past cigars	110RX	70RX	22
81†	AMI	176	—	—	—	91	269	+	132	78	25
81†	•HX	191IH	25IH	94IH	0.73	362IH	—	–	146	66	26
81†	•CHF	236IH	27IH	166IH	0.84	214IH	—	chews	96	54	27
81†	•HX	229	70	137	0.49	108	79	past	140	76	16
82†	•HX	302	58	202	0.71	207	299	past	128	72	23
82†	HX	244	—	—	—	113	116	–	156	88	26
83†	•CHF	200	34	157	0.78	47	—	pipe	144	80	24
83†	SUD	—	—	—	—	—	—	past	168	80	25
84	•AP	241	—	—	—	172	119	chews	152	92	24
84†	•AP	232	49	154	0.68	146	170	past	170	94	21
84†	HX	278	59	193	0.69	132	80	past	122	64	22
85†	AMI	202	—	—	—	100	—	–	146	80	21
85†	HX	190	31	113	0.73	232	—	past	160	84	25
86	CHF	185	58	107	0.46	98	—	past	144	80	30
87	CHF	180IH	—	—	—	93IH	169IH	–	184	92	26
87†	•HX	280	—	—	—	196	342	past	200	100	25
90†	•AP	248	48	182	0.74	91	146	–	138	70	26

TABLE 7

Male ASBD.

Age	ASBD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
45†	•HX	188	34	92	0.63	310	—	+	128	78	27
48	•HX	173IH	54IH	92IH	0.41	133IH	—	+	94	66	15
50†	•ACS	213	43	154	0.72	80	80	+	130	76	19
50	•TIA	—	—	—	—	—	—	+	142	100	22
53	ACS	200	—	—	—	144	93	+	160	98	22
55	HX	193	26	147	0.82	101	107	past	124	56	31
56	•HX	246	51	162	0.69	167	99	+	148	92	26
56†	TCVA	152IH	42IH	80IH	0.48	151IH	D	past	210IH	100IH	—
56	TCVA	182	39	115	0.66	138	312RX	+	128RX	60RX	21
57†	HX	247	42	176	0.76	146	—	+	160	82	28
57	TCVA	192	42	125	0.66	126	108	+	128	80	25
58	•TIA	247	—	—	—	614	607	past	118	78	29
59†	•TCVA	270	—	—	—	263	136D	+	162	90	31
61†	•ACS	301	49	207	0.76	223	112	+	166	104	26
62	•TIA	192	—	—	—	124	78	past	154	94	33
64†	•ACS	214	—	—	—	150	93	pipe	154	84	28
65	ACS	—	—	—	—	—	D	+	156RX	76RX	29
65	HX	154	45	97	0.54	59	125	+	150RX	88RX	—
66	•HX	240	38	160	0.76	212	114	past	140	70	25
66	ACS	330	73	229	0.68	141	88	+	130	72	27
66	•HX	263	42	188	0.78	163	125	past	186RX	42RX	23
67	ACS	149	48	78	0.38	117	91	past	132RX	82RX	24
68†	•TCVA	310	—	—	—	126	108	+	168	88	26
68†	•HX	—	—	—	—	—	—	past	110	88	—
69†	•TIA	214	—	—	—	293	416	–	130	82	27
69	•TIA	151IH	31IH	85IH	0.64	177IH	—	past	160RX	86RX	24
69	•ACS	207	35	153	0.77	93	107	–	104	48	30
70	•ACS	354RX	—	—	—	278RX	90	past	122	80	26
70†	•TCVA	230	25	—	—	917	388	past	168	106	37
70	TCVA	225IH	34IH	136IH	0.75	275IH	—	–	180IH	100IH	—
70	•HX	—	—	—	—	—	—	past	130RX	70RX	32
71	•TCVA	244	—	—	—	193	94	past	160RX	92RX	34
72†	•TIA	302	58	202	0.71	207	299	past	128	72	23
72†	•TCVA	256	49	186	0.74	103	—	+	174	78	29
75	•HX	211	20	—	—	627	—	past	126RX	60RX	27
73†	•TCVA	169IH	—	—	—	—	—	+	188	100	28
73†	•HX	—	—	—	—	—	—	–	148	102	—
73†	•ACS	263	38	196	0.81	146	133	past	144	76	29

TABLE 7 (Continued)

Age	ASBD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
73	•HX	212	47	138	0.66	137	102	past	168RX	100RX	27
73†	•HX	168RX	41RX	73RX	0.44	270RX	—	past	112RX	78RX	27
74†	•TCVA	264	41	175	0.77	241	140	past	220	108	28
74	•ACS	184IH	25IH	110IH	0.77	244IH	D	pipe	132	76	33
74	HX	141	47	68	0.31	130	155	past	156	88	28
75†	•HX	236IH	27IH	166IH	0.84	214IH	—	chews	96	54	27
76†	•HX	242IH	34IH	136IH	0.75	360IH	—	+	128RX	80RX	34
76†	•HX	257	36	170	0.79	256	161	past cigars	134	80	28
78†	•HX	271	44	201	0.78	130	—	past	186	100	28
78	•ACS	270	33	194	0.83	216	266	chews	146	94	30
78	•HX	114IH	35IH	49IH	0.29	151IH	D	–	160RX	84RX	—
79†	ACS	202	48	137	0.65	87	84	–	128	72	26
79†	ACS	—	—	—	—	—	—	+	160IH	70IH	—
82†	HX	—	—	—	—	—	—	–	132	68	20
84†	•TIA	280	—	—	—	196	342	past	200	100	25
84†	•HX	173	29	86	0.66	290	123	cigars	194	96	27
85†	TCVA	240	—	—	—	150	102	past pipe	122	86	24
85†	•HX	200	34	157	0.78	47	—	pipe	144	80	24
86†	TIA	—	—	—	—	—	—	chews	150	104	28
88†	•TCVA	248	48	182	0.74	91	146	–	138	70	26
89†	TIA	283	80	170	0.53	166	100	–	162	80	22
90†	HX	161	38	99	0.62	120	—	–	102	68	—

TABLE 8

Male ASVD.

Age	ASVD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
46†	TAA	—	—	—	—	—	—	+	198RXIH	142RXIH	—
47	HX	155	27	104	0.74	119	—	+	110	68	—
52†	•ASPVD	212	35	138	0.75	197	—	+	132RX	72RX	28
53	•AAA	318	39	232	0.83	235	95	+	110	80	27
55†	•AAA	304	—	—	—	360	181	+	190	104	39
58	AAA	187	34	118	0.71	174	—	+	130	86	25
61†	•AAA	301	49	207	0.76	223	112	+	166	104	26
63†	•ASPVD	261	—	—	—	105	115	past	158	90	27
64†	•ASPVD	214	—	—	—	150	93	pipe	154	84	28
64†	ASPVD	200	—	—	—	212	66	+	180	92	28
66†	•ASPVD	264	42	190	0.78	160	103	+	190	98	31

TABLE 8 (Continued)

Age	ASBD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
67	•AAA	207	35	153	0.77	93	107	–	104	48	30
68†	•TAA	356	—	—	—	278	225	+	180	100	27
68†	•ASPVD	230	25	—	—	917	388	past	168	106	37
69†	•ASPVD	173	—	—	—	93	162	pipe	162RX	84RX	24
69†	•ASPVD	—	—	—	—	—	—	past	110	88	—
70	•AAA	354RX	—	—	—	278RX	90	past	122	80	26
71	•AAA	243	—	—	—	225	87	+	138	82	20
72†	•ASPVD	214	—	—	—	293	416	–	130	82	27
73†	•ASPVD	163	32	94	0.66	183	326RX	chews	150RX	80RX	32
74†	•ASPVD	126	52	62	0.16	61	89	+	108	60	24
75	•ASPVD	241	—	—	—	172	119	chews	152	92	24
75	•ASPVD	211	20	—	—	627	—	past	126RX	60RX	27
76†	•AAA	252	47	171	0.73	169	198	past	140	80	—
76†	•HX	257	36	170	0.79	256	161	past cigars	134	80	28
77	HX	—	—	—	—	—	—	+	140	74	26
78†	•AAA	256	49	186	0.74	103	—	+	174	78	29
78	•AAA	270	33	194	0.83	216	266	–	146	94	30
78†	•ASPVD	263	38	196	0.81	146	133	past	144	76	29
79	•HX	178RX	37RX	124RX	0.70	86RX	—	past cigars	110RX	70RX	22
80†	ASPVD	206	54	125	0.57	134	171	+	118	80	—
82†	•ASPVD	302	58	202	0.71	207	299	past	128	72	23
82	ASPVD	222	46	157	0.71	96	—	–	120RX	80RX	26
83†	•ASPVD	191IH	25IH	94IH	0.73	362IH	—	–	146	66	26
84	•AAA	117	34	73	0.53	52	91	past cigars	146	80	25
84†	•AAA	173	29	86	0.66	290	123	cigars	194	96	27
84†	•AAA	229	70	137	0.49	108	79	past	140	76	16
87†	•ASPVD	232	49	154	0.68	146	79	past	170	94	21
88†	•AAA	248	48	182	0.74	91	146	–	138	70	26

TABLE 9

Female ASHD.

Age	ASVD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
39	HX	200	22	156	0.86	138	119	+	200	98	46
41	AP	252	50	146	0.66	281	—	+	126	80	27
42	AP	271RX	62RX	196RX	0.68	66RX	97	–	122	60	27
44	AP	264	—	—	—	72	70	–	110	76	28
45	AP	304	—	—	—	94	498	–	108	74	24

TABLE 9 (Continued)

Age	ASBD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
46	AP	285	49	158	0.69	391	108	+	94	70	28
47	AP	226	70	128	0.45	140	69	+	146	98	30
47	HX	—	—	—	—	—	—	–	118	60	33
48	ACI	219	—	—	—	129	101	–	144	90	30
49	AP	237	67	152	0.56	88	129	–	122RX	74RX	39
52	+Treadmill	228	—	—	—	217	67	+	152	98	26
52	AP	246	48	123	0.61	375	101	past	172	104	31
53†	•HX	222	—	—	—	330	146D	+	164	86	18
53	•AP	318	56	215	0.74	235	140	–	224	130	40
54†	HX	188	—	—	—	251	166RX	+	154	82	29
54	HX	341IH	—	—	—	—	—	+	152RX	98RX	31
54	AMI	276	65	193	0.66	91	—	–	160	98	—
55	HX	272	76	176	0.57	100	55	past	130	74	21
55	HX	—	—	—	—	—	—	–	168RX	82RX	27
56	HX	304	40	216	0.81	239	153	–	140	88	24
56†	HX	295	39	195	0.80	353	383	+	142RX	80RX	35
56	CHF	256	36	189	0.81	156	100	past	158	80	42
56	HX	217	56	135	0.59	132	106	+	126	74	22
57	AP	246	—	—	—	112	130	–	132	80	25
57	AP	219	—	—	—	156	86	–	132	84	36
57	HX	—	—	—	—	—	—	+	158RX	90RX	43
57	AP	312	38	222	0.83	283	—	+	164	58	33
58	HX	210	—	—	—	313	136	–	230	110	34
58†	AMI	274	—	—	—	270	1070	–	140	64	24
58	AP	267	29	202	0.86	182	78	past	120	80	41
58	ACI	381	96	258	0.63	137	—	–	180	94	21
58	•CHF	239	81	141	0.43	85	—	+	102	68	18
59	AP	220	—	—	—	160	112	+	110	72	22
59†	AMI	204	—	—	—	125	1150	+	190	112	35
59†	+Treadmill	290	—	—	—	182	167	–	190	134	35
60	AP	230	—	—	—	145	59	–	148	80	25
60	AP	237	—	—	—	388	102	–	142	80	31
60	AP	246	—	—	—	608	214	past	140	88	31
60	+Treadmill	233	46	141	0.67	229	93	–	106	62	25
60†	AMI	280	—	—	—	110	142D	+	138	92	33
60	AP	254	48	156	0.69	250	293	–	142RX	90RX	33
60	+Treadmill	185RX	70RX	70RX	0.00	227RX	122	–	160RX	88RX	28
61	AP	433	54	294	0.82	423	136	+	162	100	25
61†	CHF	337	49	250	0.89	190	—	–	102RX	66RX	23

TABLE 9 (Continued)

Age	ASBD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
62	HX	235	—	—	—	92	94	–	150	86	26
62	•HX	265	55	185	0.70	125	101	+	172RX	98RX	25
63	HX	186	—	—	—	196	270RX	–	118	78	28
63†	•HX	308	—	—	—	248	—	+	136	90	27
63†	HX	144	—	—	—	248	115	past	154	104	39
63†	AMI	273	—	—	—	295	300	–	158	86	28
63	•CHF	292	68	208	0.67	81	—	+	112	70	16
63	AP	175	33	97	0.67	229	278RX	–	128RX	80RX	41
63	•HX	—	—	—	—	—	D	past	90RX	60RX	21
64	AMI	208	45	151	0.70	60	153D	–	150	74	25
64	HX	—	—	—	—	—	D	–	92RX	54RX	25
64†	HX	—	—	—	—	—	—	+	118IH	70IH	—
64	HX	—	—	—	—	—	—	+	100RX	62RX	19
65†	CHF	295	51	186	0.73	292	—	+	118	78	22
66	•HX	242	55	177	0.69	65	—	past	118	78	22
66	HX	276	36	206	0.83	172	106	–	160RX	80RX	29
67	AP	229	46	137	0.66	231	108	–	176	84	29
68†	AMI	318IH	34IH	194IH	0.82	451IH	D	–	144	96	25
68	AP	217	34	136	0.75	233	124	past	122	62	31
68	HX	158	30	102	0.71	130	278	–	192	80	31
68	CHF	481	43	362	0.88	217	78	–	168RX	90RX	43
69†	•CHF	171IH	39IH	107IH	0.64	125IH	D	–	186	104	25
69†	HX	259IH	63IH	176IH	0.64	100IH	—	past	124	86	24
69	HX	179	27	83	0.67	343	157	past	158	94	35
69†	•HX	263	33	161	0.80	347	417	+	150	76	33
69	+Treadmill	319	50	215	0.77	269	192	–	158	72	22
69†	HX	—	—	—	—	—	—	+	152RXIH	90RXIH	—
69	AMI	—	—	—	—	—	—	+	88RX	68RX	33
69	AP	294IH	44IH	209IH	0.79	203IH	84IH	–	130	80	28
69	AP	298	38	166	0.77	470	134	–	120RX	82RX	39
69	AP	182	—	—	—	101	95	–	110	70	21
70†	HX	238	—	—	—	163	86	+	138	82	15
70	•CHF	284	32	203	0.84	246	128	–	186	114	31
70	HX	—	—	—	—	—	—	–	156RX	96RX	34
70	AP	218	93	99	0.06	128	107	–	152	94	36
70	HX	324	57	218	0.74	246	82	–	148	80	29
70	HX	177	32	94	0.66	255	146	–	128RX	80RX	23
71†	AMI	240	—	—	—	139	87	–	178	90	28
71†	AMI	286	—	—	—	166	126D	–	184	90	33

TABLE 9 (Continued)

Age	ASBD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
71	HX	219IH	44IH	145IH	0.70	148IH	D	past	140	80	34
71	•AP	247	71	146	0.51	150	103	+	126	76	18
72	HX	196	—	—	—	202	492	past	132	62	27
72	HX	190	—	—	—	81	81	past	138	74	23
72	HX	244	74	144	0.49	128	—	–	120	68	21
73	•AP	152	40	76	0.47	179	—	+	136	70	16
73	•AP	304	—	—	—	213	141D	–	184	88	30
73†	•AMI	216	66	114	0.42	178	117	–	160	76	31
73	HX	—	—	—	—	—	D	past	130	60	32
74†	CHF	277	25	—	—	787	492	past	132	64	28
74†	AMI	—	—	—	—	—	—	unkown	112	70	21
74†	AP	216	—	—	—	145	240	–	194	96	35
74	HX	274	67	184	0.64	117	92	–	138	78	28
74	AP	218	48	142	0.66	138	134	–	148	78	22
74†	•AP	351	74	213	0.65	321	109	–	156	80	30
74	AMI	268	58	184	0.68	132	—	+	148RX	60RX	20
75†	•AP	293	—	—	—	162	103	–	180	110	28
75	•HX	187	65	104	0.38	88	78	–	156	90	26
75	•HX	144*	35*	102*	0.66	41*	101	–	130	88	20
75	HX	276	—	—	—	131	52	–	190	88	28
75	AP	267IH	44IH	204IH	0.78	94IH	—	past	120	74	17
75	•HX	—	—	—	—	—	D	–	118	60	24
76	•CHF	233	—	—	—	239	118	–	156	90	26
76	HX	314	90	200	0.55	118	94	+	210	106	29
76	HX	247	62	163	0.62	110	78	+	126	76	18
76†	AP	—	—	—	—	—	D	+	116	84	21
77	CHF	168IH	35IH	108IH	0.67	139IH	D	–	184RX	98RX	32
77	HX	214	58	136	0.57	99	—	–	154RX	88RX	30
77	AP	315	—	—	—	234	111	–	114	74	22
77	CHF	199	42	—	—	—	—	–	174	70	37
77†	AMI	—	—	—	—	—	D	–	180RX	110RX	32
77†	ACI	—	—	—	—	—	—		110	84	—
77	AMI	—	—	—	—	—	—	+	122	70	24
77	•CHF	—	—	—	—	—	106	–	130RX	62RX	30
77†	AMI	(C_T ELEVATED, ON MEVACOR)				—	D	past	120RXIH	86RXIH	—
78	HX	282	—	—	—	308	116	–	178	100	27
78†	AMI	224	55	150	0.63	94	184	–	172RX	80RX	25
78	HX	268IH	—	—	—	179IH	—	–	120RX	64RX	25
78	AP	150IH	51IH	8IH	0.41	67IH	—	–	128	80	—

TABLE 9 (Continued)

Age	ASBD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
78†	HX	265IH	52IH	168IH	0.69	225IH	D	–	184RX	86RX	36
78	HX	247IH	60IH	168IH	0.64	94IH	—	–	164	74	22
78	AP	232	72	132	0.45	139	136	–	144	86	28
78†	•CHF	252	82	154	0.47	82	63	–	174	100	24
78	AP	220	36	132	0.73	262	300	past	118RX	68RX	26
79†	•CHF	—	—	—	—	—	D	–	148	82	26
79	•AMI	290	41	201	0.80	238	101	past	190	88	23
80†	•CHF	230RXIH	—	—	—	194RXIH	144IH	past	168RX	108RX	—
80†	CHF	190	—	—	—	130	—	–	188	110	23
80	•AP	321	48	235	0.80	192	79	–	134	66	23
81†	•AP	206	—	—	—	182	—	–	198RX	94RX	30
81	•HX	—	—	—	—	—	D	–	130RX	80RX	28
81	AP	321IH	112IH	177IH	0.37	159IH	—	past	124RX	64RX	30
81	•HX	212	56	138	0.59	89	120	past	138RX	80RX	35
82†	CHF	286	—	—	—	155	89	–	176	102	24
82†	•CHF	228	—	—	—	174	111D	–	160	70	21
82†	•CHF	368	56	261	0.79	255	D	–	178	66	38
82	•CHF	205	48	142	0.66	92	162	–	148	90	28
83†	AP	266	51	154	0.67	307	109	–	170RX	92RX	30
83	CHF	—	—	—	—	—	—	–	152	88	19
83	HX	158	52	93	0.44	65	—	past	156	82	30
83	HX	—	—	—	—	—	—	past	164RX	102RX	24
84	HX	250	48	169	0.72	166	97	–	190	100	30
84†	CHF	218	87	113	0.23	90	—	–	122RX	74RX	19
84	AP	211	46	115	0.60	249	—	–	132RX	74RX	19
85†	•CHF	256	—	—	—	218	222	–	142	84	33
85†	HX	227	71	133	0.47	116	154	–	180	104	21
85†	•CHF	320	63	227	0.72	151	121	–	160	68	29
85	HX	239	52	149	0.65	188	—	–	168	90	28
85†	CHF	—	—	—	—	—	—	–	160	74	15
86†	•HX	244	—	—	—	105	122	–	140	72	24
86	CHF	246	42	171	0.75	166	—	–	160	80	22
86†	AMI	—	—	—	—	—	—	–	184	142	22
86†	CHF	167	57	97	0.41	63	97	–	112RX	64RX	—
86†	•AP	315	58	222	0.74	175	174D	–	182RX	72RX	23
87	HX	263	51	171	0.70	258	255	–	168RX	80RX	26
88	•HX	—	—	—	—	—	—	–	158	80	—
89†	•CHF	218	105	101	–0.04	59	87	–	104	60	20
89	•CHF	241	62	142	0.56	184	191	–	176	102	—

TABLE 9 (Continued)

Age	ASBD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
89†	•CHF	227	51	135	0.62	204	287	–	158	80	37
90†	•CHF	262	97	138	0.30	134	—	past	144	66	20
90†	CHF	—	—	—	—	—	D	–	124	82	—
92†	CHF	—	—	—	—	—	—	–	156	72	20
92	•HX	—	—	—	—	—	—	–	124	82	—
96	CHF	232	63	149	0.58	98	95	–	122	76	24

TABLE 10

Female ASBD.

Age	ASBD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
47	HX	280	50	169	0.70	305	99	+	104	66	31
51	HCVA	284	52	170	0.69	309	200	+	180	110	27
53	•TCVA	318	56	215	0.74	235	140	–	224	130	40
56†	TCVA	271	49	175	0.72	233	D	+	220	118	—
62	HX	188	72	105	0.31	57	—	–	118	84	22
62	•HX	265	55	185	0.70	125	101	+	172RX	98RX	25
63	•HX	—	—	—	—	—	—	past	90RX	60RX	21
64	TCVA	186	40	110	0.64	181	116	past	150RX	100RX	59
65	TCVA	250	66	155	0.59	154	—	+	178	80	19
66†	•TCVA	222	—	—	—	330	146	+	164	86	18
66	•TIA	292	68	208	0.67	81	—	+	112	70	16
66	•HX	242	55	177	0.69	65	—	past	118	78	22
67†	•HX	293	—	—	—	162	103	–	180	110	28
68†	HX	268	—	—	—	119	132	+	142RX	80RX	18
69	•TIA	291	—	—	—	224	75	+	102	70	22
69†	•TCVA	263	33	161	0.80	347	417	+	150	76	33
71	TIA	212	—	—	—	150	113	–	182IH	94IH	31IH
73	•ACS	304	—	—	—	213	141	–	184	88	30
73	•ACS	290	41	201	0.80	238	101	past	190	88	23
74	•ACS	152	40	76	0.47	179	—	+	136	70	16
74	TCVA	264	51	198	0.74	93	—	–	118RX	80RX	34
75	•TIA	144	35	102	0.66	41	101	–	130	88	20
75	•HX	—	—	—	—	—	—	–	118	60	24
75	TCVA	—	—	—	—	—	—	–	160	88	38
76†	•TCVA	216	66	114	0.42	178	117	–	160	76	31
76	•TIA	284	32	203	0.84	246	128	–	186	114	31

TABLE 10 (Continued)

Age	ASBD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
76†	•ACS	351	74	213	0.65	321	109	–	156	80	30
76†	HCVA	229IH	46IH	146IH	0.68	187IH	—	past	170IH	86IH	—
77	•HX	184	39	113	0.65	162	—	past	144RX	80RX	22
77	•ACS	—	—	—	—	—	106	–	130RX	62RX	30
77†	TCVA	—	—	—	—	—	—	–	138	74	—
79	TCVA	232	—	—	—	215	117	–	134	80	33
79	•HX	321	48	235	0.80	192	79	–	134	66	23
79†	•HX	368	56	261	0.79	255	—	–	178	66	38
79†	•TIA	252	82	154	0.47	82	63	–	174	100	24
80†	HX	213IH	39IH	132IH	0.70	226IH	—	–	120	60	—
81	TIA	261	—	—	—	160	99	+	174	78	26
81†	•HX	206	—	—	—	112	—	–	198RX	94RX	30
81	•HX	—	—	—	—	—	—	–	130RX	80RX	28
82†	•TCVA	228	—	—	—	174	111	–	160	70	21
82†	•HX	171IH	39IH	107IH	0.64	125IH	—	–	186	104	25
83†	TIA	145	41	87	0.53	86	107	past	170RX	120RX	29
83†	•TCVA	230	—	—	—	194	144	past	168RX	108RX	—
83†	TIA	265	67	189	0.65	44	—	–	190RX	90RX	—
85	•TCVA	187	65	104	0.38	88	78	–	156	90	26
85	•TIA	205	48	142	0.66	92	162	–	148	90	28
86†	•HX	244	—	—	—	105	122	–	140	72	24
86†	•HX	315	58	222	0.74	175	174	–	182RX	72RX	23
87	•TCVA	241	62	142	0.56	184	191	–	176	102	—
88	TCVA	236	70	150	0.53	80	78	–	154	76	25
88	•HX	—	—	—	—	—	—	–	158	80	—
91†	•TCVA	227	51	135	0.62	204	287	–	158	80	27
92†	•TIA	262	97	138	0.30	134	—	past	144	66	20
92	•HX	—	—	—	—	—	—	–	124	82	—
94†	•TCVA	218	105	101	0.04	59	87	–	104	60	20

TABLE 11

Female ASVD.

Age	ASVD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
55	ASPVD	352	44	273	0.84	173	113	+	128	60	15
58	•ASPVD	239	81	141	0.43	85	—	+	102	68	18
66†	•HX	222	—	—	—	330	146D	+	164	86	18

TABLE 11 (Continued)

Age	ASBD	C_T	HDL	LDL	CRF	TG	PSL	Cigarettes	SBP	DBP	BMI
66	•ASPVD	242	55	177	0.69	65	—	past	118	78	22
68	•ASPVD	296	—	—	—	224	75	+	102	70	22
68†	•AAA	308	—	—	—	248	72	+	136	90	27
70	•ASPVD	233	—	—	—	239	118	–	156	90	26
74	•HX	144+	35+	102+	0.66	41+	101	–	130	88	20
78	•ASPVD	247	71	146	0.51	150	103	+	126	76	18
79	•ASPVD	290	41	201	0.80	238	101	past	190	88	23
80†	•ASPVD	—	—	—	—	—	—	–	148	82	26
80	AAA	225	30	—	—	1030	350	–	130RX	72RX	24
81	•ASPVD	184	39	113	0.65	162	—	past	144RX	80RX	22
81	ASPVD	222	63	140	0.55	93	—	–	180	118	29
82	•ASPVD	212	56	138	0.59	89	120	past	138RX	80RX	35
83	•ASPVD	—	—	—	—	—	—	past	164RX	102RX	24
83	ASPVD	237	60	141	0.57	180	136	–	118RX	68RX	24
85†	ASPVD	230	—	—	—	144	115	–	170	100	21
85†	•ASPVD	256	—	—	—	218	222	–	142	84	33
88†	•ASPVD	320	63	227	0.72	151	121	–	160	68	29
89	ASPVD	192	36	125	0.71	156	116	–	102	60	26
89	•ASPVD	—	—	—	—	—	—	–	158	80	—
92	•ASPVD	—	—	—	—	—	—	–	124	82	—
92	ASPVD	—	—	—	—	—	—	–	116	58	26

APPENDIX II

Descriptions of patients whose plots fell within the minimum risk zone in Fig. 1a:

1) Plot 0.50 vs. 132 — This man is a 48 year-old treated hypertensive diabetic, who has had chronic persistent hepatitis for the last 25 years. Whenever his liver decompensated, as it did frequently over this time-frame, his lipids rose to very high levels. The CRF plot utilized represents his lipids at a time when his liver was quiescent. Had the author elected to use a CRF obtained when his liver had been decompensated, the CRF would have been above the line. Moreover, the SBP used was the value obtained on his first office visit, after his BP had been treated. Had the author elected to disregard the study guidelines and use a BP obtained prior to his entry into the study, the untreated BP value would have been much higher and again the plot would have been well above the line. He required coronary artery bypass surgery, but since then has done well.

2) Plot 0.06 vs. 152 — This 70 year-old woman is 100 lbs overweight. Her husband, a heavy cigarette smoker, died slowly over a two-year period, and the stress of his slow demise from COPD and then from lung cancer caused her to develop angina and congestive heart failure. After he died, she adapted to his death, her symptoms resolved, and she was taken off her medication. Since that time she has not had any more ASD symptomatology and is not limited in her activity except by a case of persistent bursitis. She is now 78 years old. It is the opinion of the author that this woman does not have ASHD, but rather her heart had no cardiac reserve with which to respond to the catecholamine bombardment when she was under tremendous stress, and so underwent decompensation. The lack of cardiac reserve is directly attributed to her obesity.

3) Plot 0.29 vs. 160 — This 78 year-old man entered the BGS having already been treated for hypertension. He had a history of ASHD.

4) Plot 0.49 vs. 120 — This 72 year-old woman entered the BGS with a history that a few years earlier she had been ill in bed for about three weeks. A heavy snow had fallen and the patient had gone out to shovel her driveway. She had half finished her job when she experienced severe pain and collapsed to the ground. When she was capable of doing so, she crawled back into her house and went to bed. An EKG done a few days later showed an old myocardial infarction. She is now 78 years, and has recurrent chest pains, relieved by nitroglycerin.

5) Plot 0.41 vs. 128 — This 78 year-old woman is bed-ridden post-stroke and has an extremely labile emotional state. She also has anginal symptoms, relieved by nitroglycerin. It appears that her symptoms are at least in part the result of a coronary vasospasm.

6) Plot 0.45 vs. 144 — This 78 year-old woman has angina of effort, relieved by nitroglycerin, which she uses time to time. She is now 83 years old and is doing well.

7) Plot 0.70 vs. 110 — This 79 year-old man was presented to the BGS with an acute myocardial infarction and rupture of the myocardium posteriorly. He survived on conservative treatment. In 1976 he suffered, at age 59 years, an aortic aneurysm. At that time his cholesterol was 276 mg/dl. He subsequently went on a low cholesterol diet. His blood pressure was maintained at

APPENDIX II (Continued)

100-110 mmHG systolic by medication as part of the therapy of his myocardial pseudoaneurysm.

8) Plot 0.56 vs. 122 — This 49 year-old woman was diagnosed by another physician as having angina pectoris. The author interviewed the former patient and concurred with her current physician's diagnosis. However, no treadmill test was done to confirm the diagnosis. She is now a hypertensive diabetic, but the plot represents the data when she first presented to the BGS.

9) Plot 0.00 vs. 160 — This 60 year-old woman developed typical chest pain. A treadmill test was positive, though a thallium study was normal. Consultation with a cardiologist indicated that the treadmill results strongly warranted an angiogram, which to date has not been done because the patient, who feels well, is unwilling. Her lipid data were obtained at BGS presentation when she was already on hormone replacement therapy, which is known to influence lipids. Her high blood pressure was already being treated at BGS presentation.

10) Plot 0.31 vs. 118 — This 62 year-old lady had a CAT scan for headaches and was found to have had two strokes, neither of which she nor the author had been aware. The old cerebral infarcts were incidental findings. Historical investigation revealed that both her mother and her maternal grandmother had suffered strokes. To date, detailed investigation, under the supervision of a neurologist, has failed to reveal a cause. The patient has Parkinson's disease and takes multiple medications for this condition. Her lipid data was obtained while she was on these medications.

In the first 16 years of the BGS, these are the only known exceptions below the line. The ASD of these individuals is relatively mild. All are still alive, some now in their eighties.

APPENDIX III

The medical research literature upon which the BGS is based supports the use of the CRF as the optimal lipid predictor. There are now six major epidemiological studies and nine angiographic studies that provide a basis for this statement. A brief description of each of these studies is now presented.

1) Lipid Research Clinics Program (LRC): The LRC studied 3,806 men with Type II Hyperlipoproteinemia. The lowest C_T entry was 265 mg/dl. This was a primary prevention trial. Using Questran™, patients lowered their C_T by 13.4% and LDL by 20.3% . The average LDL prior to therapy, which also included a low cholesterol and saturated fat diet, was 216 mg/dl. With therapy the average LDL fell to 175 mg/dl, the average HDL rose to 47 mg/dl, and the average CRF fell to 73%. As a result of this therapy, the treated group subsequently suffered 30% fewer definite and suspect cardiac deaths and 15% fewer definite and suspected non-fatal heart attacks. Of interest is the fact that this benefit was not evident until the third year of the study (Lipid Research Clinics 1984).

2) Helsinki Heart Study (HHS): The HHS examined 4,081 men with dyslipidemia using its entrance criterion a "non-HDL" cholesterol of 199 mg/dl. This was also a primary prevention trial. The HHS used Lopid™, which lowers LDL but also raises HDL, in the treatment arm of the study. Both treatment and placebo groups were placed on a low cholesterol and low saturated fat diet, were advised to exercise and lose weight, and were told to stop smoking. The treatment group lowered its average LDL from 189 mg/dl to 174 mg/dl at the end of the treatment five years later; HDL had risen from 47 mg/dl to 51 mg/dl; CRF had fallen from 75% to 71%. Over the study period the treatment group had a 34% drop in subsequent ASD, primarily in non-fatal myocardial infarctions. The cardiac ASD fatality rate was 5.3 per thousand in the treatment group versus 6.4 per thousand in the placebo group. As in the LRC, no benefit was seen until the third year of the study (Frick et al. 1987).

3) National Heart, Lung, and Blood Institute Type II Coronary Intervention Study: Kelsey discussed this trial which was an attempt to reverse angiographically documented ASHD by diet and medication. This therapy dropped mean LDL levels from 242 mg/dl to 178 mg/dl and raised mean HDL levels from 38 mg/dl to 41 mg/dl. The average CRF fell from 84% to 77%. The control group was treated only with diet. The control group's plaques progressed in 49% of cases, whereas progression was noted in only 32% of the treated patients. Regression, both probable and definite, occurred in only four of the treated patients and did not differ from the control group (Kelsey 1986). Levy, who conducted the study, comments as follows: "Using coronary angiography, there is evidence that an increase in HDL, a decrease in LDL, or preferably both, could delay or prevent coronary artery disease progression." Levy further noted that the least progression and some regression of angiographically documented ASHD occurs in groups showing the most decrease in LDL and the most increase in HDL (Kelsey 1986).

4) E. A. Nikkila: Nikkila studied patients with ASHD, treating them with diet and medication. Serial angiograms were done. No cases of lesion regression were seen, but those who did not show progression brought their LDL levels down to 159 mg/dl and their HDL levels up to 45 mg/dl; those with slight progression brought their LDL levels down to 173 mg/dl and their HDL levels up to 45 mg/dl; those showing severe progression had LDL levels of 185 mg/dl and HDL levels of 38 mg/dl. Respective CRFs were 72%, 74%, and 79% (Nikkila et al. 1984).

5) D. H. Blankenhorn: Blankenhorn studied patients with progressive ASHD. Treated patients were put on a stringent diet and medication (niacin and Colestipol™), whereas the control group was put on a less stringent diet. Treated patients dropped their LDLs from 170 mg/dl to 97 mg/dl and raised their HDLs from 45 mg/dl to 61 mg/dl. The CRF dropped from 74% to 37%. The control group dropped its LDL levels from 169 mg/dl to 160 mg/dl, but was not able to raise their HDL from the 44 mg/dl level; their CRF dropped minimally from 74% to 73%. On repeat angiogram, the treated group had less ASD than did the control group. Treatment produced a significant reduction in progression of ASD in native coronary arteries, both in average number of lesions that progressed per patient and in percentage of patients with new plaque formation. Treatment also significantly reduced the percentage of patients with any adverse change or new lesion in venous bypass grafts. Blankenhorn concluded: "The Cholesterol Lowering Atherosclerosis Study has demonstrated that aggressive lowering of LDL cholesterol with concomitant increase of HDL cholesterol levels produced significant benefit to both native coronary arteries and venous bypass grafts" (Blankenhorn et al. 1987).

6) L. Campeau: Campeau studied patients who had already had coronary artery bypass graft surgery. He defined two groups of patients based upon serial angiograms; one in which recognizable abnormalities did not occur in by-passed arteries or in vein by-pass grafts (Group I) and the other in which such abnormalities did occur (Group II). Treatment was nonpharmacologic. Group I patients had a drop in their LDL levels to 153 mg/dl and a rise in their HDL levels to 63 mg/dl, whereas Group II patients maintained an LDL level of 190 mg/dl and an HDL of 48 mg/dl. Respective CRF values were 59% and 75% (Campeau et al. 1984).

7) B. Lewis: Lewis studied ASD of the peripheral arteries (ASPVD) in patients aged less than 65 years. Treatment was by diet and medication, as well as advice to stop smoking. Control patients were treated by diet and smoking advice. Treatment groups resulted in a drop in LDL to levels of 151 mg/dl, a rise in HDL to levels of 58 mg/dl, and a drop in CRF to 62%. Controls dropped their LDLs only to 197 mg/dl, raised their HDLs only to 42 mg/dl, and dropped their CRFs only to 79%. Upon repeat angiography, treated patients showed one third the increase in plaque areas showed by control patients. Furthermore, twice as many treated patients showed a decrease in their edge-irregularity index as did controls. Finally, almost three times as many controls showed progression as did treated patients (Lewis 1985).

8) R. G. M. Duffield: Duffield studied patients with ASPVD. All patients were told to stop smoking and lose weight. Treated patients were also given a special diet and medication. Treatment groups lowered their LDLs from 209 mg/dl to 151 mg/dl and raised their HDLs from 47 mg/dl to 60 mg/dl. The CRF fell from 78% to 60%. Upon follow-up angiogram, 33% of treated patients showed a decrease in plaque edge-irregularity versus 17% of controls . Only 6.9% of treated patients showed progression versus 17.3% of controls (Duffield et al. 1983).

APPENDIX III (Continued)

9) G. Brown: Brown studied 146 men with a family history of ASHD, Apo-B levels of 125 mg/dl or higher, and established ASHD (a single 50% lesion or three 30% lesions on angiograms). Three treatment regimens were given: placebo/Colestid™, Mevacor™/Colestid™, and niacin/Colestid™ (Groups 3, 2, and 1 respectively) . Group 3 patients lowered their LDL levels from 4.53 mmoles/L to 4.2 mmoles/L (176 mg/dl to 163 mg/dl), raised their HDL levels from 0.98 mmoles/L to 1.04 mmoles/L (38 mg/dl to 40 mg/dl) and lowered their CRF from 0.78 to 0.75. Group 2 patients lowered their LDL levels from 5.08 mmoles/L to 2.77 mmoles/L (198 mg/dl to 108 mg/dl), raised HDL levels from 0.91 mmoles/L to 1.06 mmoles/L (35 mg/dl to 41 mg/dl), lowered their CRFs from 0.82 to 0.62. Group 3 patients lowered their LDL levels from 4.92 mmoles/L to 3.34 mmoles/L (191 mg/dl to 130 mg/dl), raised their HDL levels from 1.01 mmoles/L to 1.42 mmoles/L (39 mg/dl to 55 mg/dl) and lowered their CRF from 0.79 to 0.57. Serial coronary angiograms were done . After 2.5 years of therapy, regression occurred in both Groups 2 and 1, (but regression was always more pronounced in Group 1) whereas Group 3 patients had consistently worsening stenosis (See table below) (Brown et al. 1990).

	GROUP 3	GROUP 2	GROUP 1
Angiographic			
1) regression	11%	32%	39%
2) progression	46%	21%	25%
ASHD events (SUD, AMI, CABGS)	19%	6.5%	4.2%

(SUD = sudden unexpected death, AMI = acute myocardial infarction, CABGS = coronary artery bypass surgery).

10) H. Buchwald: Buchwald studied 838 male survivors of AMI. Surgical treatment (partial ileal bypass) was done in 421 patients and 417 patients were put into the control group. All patients were treated with diet therapy. The surgical group lowered its LDL levels from 4.62 mmoles/L to 2.82 mmoles/L (180 mg/dl to 110 mg/dl), raised their HDL levels from 1.03 mmoles/L to 1.06 mmoles/L (40 mg/dl to 41 mg/dl), and lowered their CRF from 0.78 to 0.63. The control group lowered their HDL levels from 1.05 mmoles/L to 1.00 mmole/L (41 mg/dl to 39 mg/dl) and did not change their CRF (0.77). AMI and ASHD deaths did not differ between the two groups until the third year, whereupon the surgical group began having fewer end points then did the control group. When all ASHD events were combined, 222 events occurred in the control group versus 160 events in the surgical group (P .00001) (Buchwald et al. 1990).

11) I. Hjerman: The Oslo Study Diet and Anti-Smoking Trial study involved 1,232 healthy men aged 40-49 years, who had a C_T in range of 280-380 mg/dl. All were normotensive and 80% were cigarette smokers. The treatment group received dietary advice and were advised to stop smoking. The control group received no treatment, however, 17% of controls stopped smoking, compared with 24% in the intervention group. The treatment group lowered their LDL from 262 to 187 mg/dl, raised their HDL from 28 to 50 mg/dl, and lowered their C_T from 0.89 to 0.73. The control group did not lower their LDLs (259 mg/dl), but did raise their HDL from 29 to 42 mg/dl, thus lowering their CRF from 0.89 to 0.84. Coincident with these changes, the treatment group had a reduction in cardiac deaths, 6.6 per thousand vs 20.1 per thousand in controls. There was no difference in AMI or CVA (Hjerman et al. 1986).

12) G. F. Neitzel: Neitzel studied patients who had undergone coronary artery bypass surgery and who required a second operation (40 patients) versus 535 patients who did not require a second operation. Those requiring a second operation had an average HDL of 38 mg/dl, an average LDL of 175 mg/dl, and an average CRF of 0.78. Those not requiring a second operation had an average HDL of 47 mg/dl, an average LDL of 150 mg/dl and an average CRF of 0.69 (Neitzel et al. 1986).

13) G. Schuler: Schuler studied men with stable angina, LDLs less than 210 mg/dl, and ASD not severe enough to prevent exercise therapy. The treatment group received a low fat, low cholesterol diet and a regular exercise program. The treated patients lowered their LDLs from 147 mg/dl to 130 mg/dl, raised their HDLs from 39 mg/dl to 40 mg/dl, and lowered their CRFs from 0.73 to 0.69. The control group had a rise in LDL from 150 to 172 mg/dl, a rise in HDL from 36 to 37 mg/dl, and a rise in CRF from 0.76 to 0.78. During the study two control patients had an AMI versus no treated patients. Treated patients had decreased myocardial ischemia on Thallium treadmill with respect to controls at one year. This implies increased myocardial perfusion in the patients with symptomatic ASHD. Physical work capacity likewise increased in treated patients, but in no control patients (Schuler et al. 1988).

14) G. Watts: Watts studied 90 men with angina or other findings of ASHD and with C_T exceeding 231 mg/dl but TG less than 355 mg/dl. The control group received the usual care; Group I patients received diet counseling, whereas Group II patients had diet counseling plus cholestyramine 8 g twice a day. The control group had a minimal change in LDL (186 mg/dl to 180 mg/dl) and no change in HDL (constant at 47 mg/dl). Group I patients lowered their LDL (193 mg/dl to 161 mg/dl) but HDL remained unchanged at 44 mg/dl. Group II patients lowered their LDL (203 mg/dl to 130 mg/dl) but also lowered their HDL (48 mg/dl to 46 mg/dl). Changes in CRF were respectively 0.75 to 0.74 (controls), 0.77 to 0.73 (Group I), and 0.76 to 0.65.(Group II). Follow-up was done by paired angiograms and clinical event determination over a follow-up time averaging 39 months. All angiographic criteria consistently worsened in the controls and consistently improved in Groups I and II, with all segments in these latter groups showing improvements including the most severe stenosis (See table below) (Watts et al. 1992).

	CONTROLS	GROUP I	GROUP II
Sudden Unexpected Death	3	1	0
Acute Myocardial Infarction	2	1	1
Coronary Artery Bypass Surgery	4	1	0
Stroke	1	0	0
Total	10	3	1
	(36%)	(11%)	(4%)

15) M. Fox: Fox studied ASD risk factors in patients who underwent coronary artery bypass surgery. He compared those who required a second operation at least six months later (Group I) vs. those who did not require a second operation (Group II). Group I patients had an LDL of 179 mg/dl, HDL of 49 mg/dl, and a CRF of 0.77, whereas Group II patients had an LDL of 172 mg/dl, HDL of 44 mg/dl, and a CRF of 0.74. More Group II patients were hypertensive (30.4% in Group II vs. 21% in Group I) (Fox et al. 1992).

APPENDIX IV

LDL Medications

1) Bile acid resins [Questran™ and Colestid™]: These agents bind cholesterol and bile acid within the gut, inhibiting cholesterol absorption and interrupting the enterohepatic circulation of the bile acids. When levels of bile acid fall, LDL receptors are induced within the hepatocytes, removing LDL from the blood to be used in bile acid synthesis (Shepherd et al. 1980). At doses of 4 g or more four times a day, these agents are very effective in lowering blood cholesterol (LDL), but also cause gastrointestinal distress with cramping, bloating, and constipation. Such effects may occur even at lower doses, especially in older individuals. The BGS therefore uses these resins only in lower dosages, often as adjuncts to other medications. Metamucil™ may be added to or substituted for the resins to reduce side-effects.

2) Nicotinic acid [Nicobid™, etc.]: This drug decreases the hepatic secretion of VLDL, thus lowering LDL and VLDL while raising HDL by another mechanism (Shepherd et al. 1979). At therapeutic doses, nicotinic acid causes flushing and itching. These sequelae can be averted or at least minimized by taking the drug in sustained release form, by taking the drug after meals, and by taking an aspirin with each nicotinic acid dose. Unfortunately, at doses of nicotinic acid required to achieve therapeutic goals—i.e., in the BGS experience, Nicobid™ 1.0-1.5 g twice a day—there is a fairly high risk of drug-

APPENDIX IV (Continued)

induced hepatitis and, in recent years after a number of such cases, nicotinic acid is no longer prescribed at such a dosage. In addition, the brand name is costly and if six capsules twice a day are used, the cost per month could be excessive. As a result, reliance is placed upon generic versions of the drug. This reduces the cost, but the treating physician must be prepared for the occasional batch of drug which appears to contain little if any active drug, as evidenced by the observation that increasing the dose of nicotinic acid sometimes results in rising LDL levels and falling HDL levels—just the opposite effect that would be expected.

3) Probucol [Lorelco™]: This drug enhances the catabolism of LDL and does so even in patients who do not possess LDL receptors in the liver, This means that probucol can act directly in the liver by inducing LDL receptors as blood levels of LDL fall or directly in the periphery by "alternative pathways" independently of any hepatic mechanism. The exact mechanism remains to be elucidated, but may involve the reticuloendothelial system and its macrophages (Steinberg 1986). BGS experience with probucol is limited to a few patients since marked drops in HDL levels occur with probucol administration. Although probucol may prevent the progression of ASD in rabbits (Kita et al. 1987), the lowering of HDL invalidates the use of CRF as predictive and therapeutic tool and limits its use in the BGS.

4) Hydroxymethylglutaryl coenzyme A reductase inhibitors [lovastatin, Mevacor™]: This drug interferes with conversion of hydroxymethylglutaryl coenzyme A to mevalonate, an early rate-limiting step in the synthesis of cholesterol (Havel et al. 1987). By inhibiting cholesterol synthesis in hepatocytes, hepatic LDL receptors are induced, internalizing circulating LDL for the synthesis of hepatocyte intracellular cholesterol. This results in a marked drop in blood levels of LDL and as an added benefit, HDL levels rise. At doses of 20-40 mg of lovastatin per day, after supper, few adverse sequelae have been noted from this drug after more than three years experience, except for the cost, which is significant. The cost of multi-drug regimens which may be necessary if lovastatin is not used, however, often significantly exceeds the expense of lovastatin. In the BGS, the preferred regimen is lovastatin 20 mg after supper with/without 4 g of bile acid resin at bedtime. This regimen has induced 100 mg drops in LDL levels in a convenient regimen which is not too expensive.

5) Female hormone replacement therapy (HRT): HRT in the BGS is defined as Premarin™ 1.25 mg daily for the first 25 days of each month, complemented by Provera™/Cycrin™ 5-10 mg daily from day 13-25. (The dose of Provera™/ Cycrin™ is usually 10 mg, but in women who have had hysterectomies, may be reduced to 5 mg if the occasion requires). HRT finds its use in peri- and postmenopausal women as a physiological treatment for hyperlipidemia of the menopause (Hirvonen et al. 1981). Following the suggestion of Tikkanen, the BGS began using HRT as primary and adjunctive therapy for the menopausal women (Tikkanen et al. 1978). The results have been most gratifying. HRT is considered the treatment of choice in appropriate patients.

HDL Medications

1) Nicotinic acid: Please see previous discussion.

2) Gemfibrozil [Lopid™]: This drug decreases hepatic secretion of VLDL and increases VLDL catabolism (Vega and Grundy 1985). As a result gemfibrozil lowers TG, has a variable effect of LDL, and usually raises HDL. Because of these beneficial effects, the BGS has utilized this drug extensively to raise low levels of HDL. In the BGS experience, gemfibrozil has had a few adverse reactions, and so, if the cheaper nicotinic acid fails to normalize HDL, the BGS does not hesitate to switch to gemfibrozil.

3) Hydroxymethylglutaryl coenzyme A reductase inhibitors: This drug may be used in HDL disorders only if other means of raising HDL have failed. In such cases, the BGS policy is to abandon the failed HDL regimen and to lower the LDL as simply and easily as possible such that the CRF is low despite the low HDL. It is hoped that this regimen will push back the onset of ASD by lowering the incoming cholesterol until other HDL drugs are available.

TABLE 12

Dyslipidemia Medications.

I. LDL MEDICATIONS

A. Bile acid resins (Questran™, Colestid™, Metamucil™)
B. Nicotinic acid (Nicobid™)
C. Probucol (Lorelco™)
D. Lovastatin (Mevacor™)
E. Hormone Replacement Therapy (HRT)

II. HDL MEDICATIONS

A. Nicotinic acid (Nicobid™)
B. Gemfibrozil (Lopid™)
C. Lovastatin (Mevacor™)